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SEMINAR ON THE NEPHROTIC SYNDROME*

J. B. KOPSTEIN, M.D.

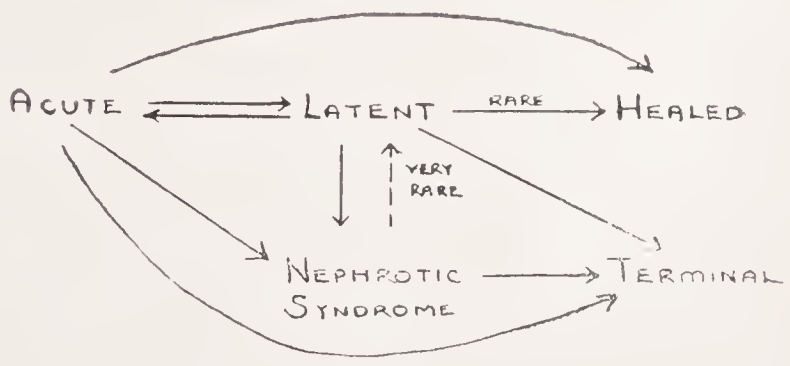
It has been over a hundred years since Richard Bright described the first of a group of renal diseases which now bear his name. One of these, the Nephrotic Syndrome, had been the subject of intense investigation for many years prior to Valhard and Fahr's classical work in 1914. And yet not only the aetiology and specific treatment remain obscure but the natural history has never been completely clarified. Thus it is with some trepidation that I begin this discussion of clinical features, natural history and some of the many theories attempting to explain the chemical pathology. First let it be clear that the syndrome under discussion is one characterized by more or less edema, proteinuria, hypoalbuminemia, hyperlipemia and hypercholesterolemia together with certain other features which may or may not be present. A marked difference of opinion exists as regards the position of the nephrotic syndrome in the general classification of renal disease.

Natural History

It may occur in association with certain systemic diseases and toxicities. It can also occur during the natural history of glomerulonephritis beginning with a recognized antecedent acute attack. At this point it is well to digress briefly to consider the various modes of progression of acute haemorrhagic glomerulonephritis. In doing so it will help to fit the Nephrotic Syndrome into the general picture. It is well known that acute nephritis may terminate in:

1. Complete recovery.
2. Death in the acute stage.
3. Death within 3-4 months after rapid progression to the terminal stage.
4. Persistence of albuminuria, hematuria together with steadily progressive diminution of renal function. This is so called latent nephritis.
5. Progression to the Nephrotic Syndrome either directly from the acute phase or via an intervening long or short latent phase.

All of this is well shown in the diagram taken from Addis and Van Slyke.



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In the latent stage the general experience has been that complete recovery very rarely occurs. The usual course of these cases is directly downhill to the terminal stage in months or years or to an intervening Nephrotic Stage with ultimate death in 6 months to 2 years after reaching this phase of the disease. Addis reports a few cases which regressed to the latent from the Nephrotic but this has not been the general experience in the literature. Thus we see the relation of latent nephritis to the Nephrotic Syndrome.

What is the relationship of the Nephrotic Syndrome to acute and chronic nephritis? The Nephrotic Syndrome may occur simultaneously and in association with acute haemorrhagic nephritis. Thus Janeway has reported a few cases in which following acute upper respiratory tract infection the child presented with gross hematuria, hypertension, minimal edema and marked proteinuria, together with other urine and blood findings intermediate between those values which are usual in the two diseases.

A typical syndrome can occur in my experience a few weeks after an episode of acute haemorrhagic nephritis. Nevertheless these may be regarded as possible accelerations of a natural history in which the nephrotic syndrome may develop simultaneously with, weeks, months or years after a recognized acute episode of nephritis.

It has been the experience of many clinicians that patients in the terminal stage of chronic nephritis often become grossly edematous. In most of these, hypertensive heart disease with failure or salt retaining nephritis must be considered. Nevertheless the Nephrotic Syndrome can occur but is unusual here in view of the fact that apart from edema its other features are not usually apparent.

In most instances however the disease develops in a child or adult who has had no history of acute nephritis and in whom the possibility of systemic diseases and toxicities can be eliminated. Three main views are held regarding this clinical type.

1. The first states that all these cases represent stages in the development of glomerulonephritis in which the acute phase was unnoticed or minimal.

2. The second maintains that there are two distinct diseases both manifested by edema, albuminuria, hypoalbuminemia and hypercholesterolemia but with the addition of haematuria, rise in NPN and rise in blood pressure in the second type. Those with this view maintain that this second type should be considered as a stage of glomerulonephritis with unrecognized acute onset while the first which they call Genuine Nephrosis or Lipoid nephrosis is entirely separate due to its excellent prognosis and lack of RBC in the urine, azotemia and rise in B.P.

3. The third view, which is becoming increasingly popular among pediatricians, considers this form of the Nephrotic Syndrome a single disease entity which is not preceded by unrecognized acute glomerulonephritis and in which edema, albumenuria and hypoproteinemia may or may not be accompanied by persistent signs of hematuria, hypertension or azotemia.

This third view implies a distinct clinical separation between the nephrotic syndrome and glomerulonephritis. It furthermore makes the term lipoid nephrosis redundant since patients may recover completely or die in renal failure. This view in my opinion best describes

the disease as seen in children and should be universally adopted.

In concluding this classification it should be emphasized that those cases without antecedent acute haemorrhagic nephritis are the commonest group. They occur chiefly in children and when such a case is encountered in a patient after the age of 25 it should be considered, for practical purposes, in the same category prognostically as those cases progressing from acute nephritis. Purposely omitted from this discussion are the multitude of names for the Nephrotic Syndrome, which have served only to confuse the issue and make clarification an extremely difficult procedure. e.g. Type 2 Nephritis of Ellis, Degenerative nephritis of Addis, and Subacute nephritis (which should be avoided at all costs). Nephrotic symptoms can occur anytime during the natural history of nephritis, not just in 3 or 4 months from the acute onset. It is primarily for this reason that "subacute nephritis" should make its exit from the terminology of this disease in a manner similar to the way leeches have disappeared from the treatment of congestive heart failure.

Clinical Features

The clinical features of the Nephrotic Syndrome. Because of the fact that it is much more common in children than in adults it is more reasonable to discuss the salient features in this age group with later mention of a few of the differences in the adult. Barnett defines the Nephrotic Syndrome as a clinical condition occurring mainly in children, manifested by edema, albuminuria, hyperlipemia, hypoproteinemia and usually but not always relatively normal levels of NPN and blood pressure with little if any hematuria. The course is chronic with remissions, exacerbations and in many instances complete recovery.

In most series approximately one half of the cases are found in the 2nd or 3rd year with the onset before the 5th year in two-thirds of the cases. This is markedly different from acute nephritis in which the peak onset is 7 or 8. There is no significant sex incidence or family history. In addition most children were in good health prior to onset with overt infection preceding the syndrome in less than one-fourth of cases.

The *onset* is nearly always insidious with edema under the eyes or rapid increase in weight as the first symptoms. An older patient may state that only a few days previously he had noticed heaviness in his legs at the end of the day or had found deep creases above his shoes when he took them off at night. The edema may remain moderate or rapidly progress to anasarca with ascites and/or hydrothorax.

The *urine* shows greater or less albuminuria which is not always in proportion to the amount of edema. Similarly, little if any edema may be accompanied by marked albuminuria in the rare case. Characteristically, there is moderate oliguria with a rise in urinary specific gravity. Under the microscope there are a large number of epithelial cells, epithelial cell casts, granular, hyaline and fatty droplet casts with many free fat droplets. Red cells may be absent, sparse, or frequent but often there is a marked fluctuation in their number.

The amount of *albumin* as already indicated varies within wide limits, the usual average being 10-20 gm. per day. Similarly hypoalbuminemia varies within wide limits although nearly always less than 215 gm. By electrophoretic methods gamma globulin is found to be reduced

and the remainder of the globulin fraction normal or raised.

Blood cholesterol is invariably raised with anywhere from 250-1000 mg.% having been reported. The BMR is low and the PBI and Radio-Iodine uptakes are also often low. Hypovolemia and an intracellular deficit of potassium are demonstrable. It is interesting to note that infusion of nephrotic patients with *Na* greatly augments potassium excretion, suggesting that this is a possible factor in potassium deficit. 17-ketosteroid excretion is reported as low with an increase in DOCA-like substances and pitressin-like factors in the urine. The VDM substance of Zwiefach and Shore is increased in the peripheral blood and edema fluid of the nephrotic.

Symptomatically nephrotic children frequently show anorexia, irritability and gastro-intestinal upsets. Their notoriously poor appetites together with loss of protein accounts at least in part for severe degrees of malnutrition which may be concealed by the edema. Gastro-intestinal upsets especially diarrhoea are common.

Minor skin irritations and infections, dilatation of the veins of the abdominal wall, rectal prolapse and umbilical herniae are said to be frequent.

Hepatomegaly occasionally occurs during the course of the disease while certain other physical signs are related to the edema. These are ascites, hydrothorax and the peculiar pallor which may be attributed at least in part to expression of blood from skin vessels by edema fluid. Respiratory difficulty from abdominal distension with or without pleural effusion may be disturbing. The clinical course of the disease shows variations which are usually if not always judged in relation to the presence or absence of edema. Although edema may be present constantly after onset, remissions often alternate with periods of severe edema.

Anemia occurs rarely during the early stages but is a constant accompaniment of the transition to the terminal stage. Frequent severe infections especially of the pneumococcal type are said to be related to the diminution of gamma globulin.

Anywhere from 60-95% of patients, according to various series, have been reported as having had remissions. Usually within 2 months, but occasionally as late as 12 months after onset, diuresis occurs spontaneously with adrenalcorticoid therapy or following severe infection. The usual upper respiratory tract infections are more commonly associated with exacerbations. As Lange has noted, diuresis frequently follows an acute attack of measles. Spontaneous remission apparently occurs less frequently for any individual patient the longer the disease progresses. The duration of remission and exacerbations is extremely variable as is the total duration of the disease which is usually measured in months or years.

For many years the literature has been permeated with articles professing to be able to distinguish the Nephrotic phase of glomerulonephritis and Lipoid Nephrosis from each. The ultimate object of such attempts was to distinguish cases which would recover from those in whom death could be anticipated sooner or later.

The basis of such distinction was founded in hematuria, rise in NPN, and rise in blood pressure which, if present, indicated a bad prognosis.

Most workers have rightfully given up this concept and, as Janeway and his colleagues have well stated, microscopic

haematuria, slight to moderate azotemia or a moderate rise in blood pressure are unreliable indices of the functional state of the kidney or subsequent course.

Regarding the course of patients with the nephrotic syndrome certain facts remain clear:

1. Children may have normal urea clearances, no hypertension and no haematuria and either recover completely or die of renal insufficiency.
2. Have all or some of these and yet eventually recover or die of renal insufficiency.

It now remains to describe the ultimate course of patients with:

1. Nephrotic Syndrome after a recognized acute episode of haemorrhagic nephritis—both children and adults.
2. Those children with the syndrome without antecedent history who do not recover.
3. Adults over the age of 25 without antecedent history.

The common denominator of all these is death.

A few persist with nephrotic symptoms and signs to the uremic end. In the vast majority these signs clear up and the patients are left with minimal albuminuria, cylindruria and edema with a rising NPN and ultimate death in uremia.

A few cases have been reported in the literature of recovery from the Nephrotic Syndrome in an adult without antecedent history. These should be regarded as clinical rarities.

Chemical Pathology

PROTEINURIA

Although it has been well established that the origin of the urinary protein is the plasma itself it remains to be clarified how this transfer occurs. Four theories exist:

The first of these postulates *failure of tubular reabsorption* of normally filtered protein. Chinard effectively refuted this theory by proving that the concentration of albumen in the glomerular filtrate in nephrotic patients far exceeds the normally accepted value of 25-30 mg.%.

2. A second theory postulated *secretion of protein* by the tubules.

3. A third theory considered the *formation of abnormal proteins* which as such were excreted. This has been effectively refuted by immunological, chemical and electrical methods which have shown the urinary albumin to be normal. In addition normal patients in whom nephrotic albumin had been injected did not excrete it.

4. We are left with the concept of *increase in glomerular permeability*. And indeed Chimard was able to show by indirect methods that albumin clearance relative to permeability to water was greatly increased in the Nephrotic Syndrome.

HYPOPROTEINEMIA

It is generally accepted that hypoproteinemia is produced as a direct consequence of massive excretion of albumin in the urine. Some have postulated that failure of albumin synthesis may play a contributory role. Nevertheless, as Whipple and Cotui and numerous other observers have shown the nephrotic patient can not only synthesize as much albumin as the normal patient but often many times as much. Indeed some Nephrotics can synthesize as much protein as they are losing in the urine.

The general consensus remains however that poor appetite, repeated infections, and massive loss do not allow an

average patient to maintain serum albumin levels for very long periods of time.

EDEMA

In 1918, A. A. Epstein first applied Starling's hypothesis to the pathogenesis of edema. This considered the edema to be a direct result of the lowering of the serum albumin with the resultant lowering of the colloid osmotic pressure and flow of fluid into the tissues. The level of serum albumin when this phenomenon occurs has been shown to be 2.5 gm.%.

Nevertheless, within the past 15 years, serious doubt has existed as to whether this is correct or even partly correct. The edema in Nephrotic patients correlates only imperfectly with serum albumin concentration. Furthermore, there occur in children and adults, instances of low albumin concentration without renal disease in which there is no edema. Addis and numerous observers thereafter have seen the edema come too soon after onset and go too quickly after cessation of proteinuria to state that one is dealing with a simple depletion phenomenon. However it is certainly unquestionable that, other things being equal, a decrease in plasma albumin must necessitate a net shift of water and smaller solutes from plasma to interstitial spaces. It is equally true that for a large expansion of the extracellular fluid to occur, the kidneys must retain a portion of the daily intake of water and sodium.

In order to account for this, excess tubular reabsorption either relative or absolute must be postulated.

A currently popular theory maintains that hypoalbuminemia leads to a net shift of water into the interstitial spaces at the expense of the intravascular water. As in the forward failure theory, this implies a diminution of renal blood flow, diminution of glomerular filtration rate and diminished filtration of sodium. The tubules reabsorb at their normal rate and hence relatively more sodium and water is retained.

In opposition however these clearance values are often within normal limits in nephrotic patients rather than reduced. To overcome this objection, primary tubular preponderance has been postulated. Thus the proximal tubules under the influence of Doca-like substances or post pituitary substances are blamed for increasing tubular reabsorption apart from the relative increase due to diminished filtration. Indeed, some observers have found these substances in increased quantities in the urine. Overactivity of renal nerves has been given by others as an explanation of increased tubular activity. It suffices to say that nothing is as yet settled.

HYPOMETABOLISM

This term is used advisedly, for these patients are not hypothyroid in the true sense for several reasons:

1. If the BMR is calculated on the basis of ideal weight there is slight or no abnormality because edema fluid is inert metabolically.

2. There are no signs or symptoms of hypothyroidism and dessicated thyroid is ineffective.

3. Hypercholesterolemia in myxoedema is not accompanied by an increase in blood lipids as it is in the nephrotic syndrome. Recent work by London using deuterium tracers has shown that the half life of this lipoid substance is increased 8-45 days more than normal in nephrotic patients. This may perhaps account for its high levels but the ultimate

reason to why it persists so long has never been satisfactorily explained.

4. A low PBI is frequent due to loss of proteins in the urine and the radio iodine uptake is frequently low in these patients. The literature offers no satisfactory explanation of these abnormalities.

Since the days of Bright the serum of patients with the Nephrotic Syndrome has been known to be opaque and milky due to the presence of lipids. These are fats of the phospholipid and neutral type. Some have postulated increased mobilization from the reservoirs, others postulate failure of removal by the liver as the cause of this abnormally high plasma lipid concentration. In short there is no evidence for either view at present.

In conclusion, an attempt has been made to outline a useful clinical concept of the Nephrotic Syndrome, to indicate some of its clinical features and a few of the theories attempting to explain its chemical pathology. This is also an appeal for uniformity of nomenclature, the lack of which makes study of the literature and, more important, the study of patients, an extremely difficult procedure.

The hardest conviction to get into the mind of a beginner is that the education upon which he is engaged is not a college course, not a medical course, but a life course, for which the work of a few years under teachers is but a preparation.—Osler.

THE ETIOLOGY AND PATHOLOGY OF THE NEPHROTIC SYNDROME*

R. J. BAIRD, 5T4

The nephrotic syndrome is a clinical term which is used to designate the occurrence of gross generalised edema associated with oliguria, proteinuria, hypoalbuminemia, hypercholesterolemia and lipemia. Hypertension, hematuria, and renal insufficiency are usually transient or absent.

Before embarking on any discussion of either its etiology or pathology, it must be realized that the syndrome is not characteristic of any specific disease, but rather is found in association with and as a complication of a variety of disorders. With this fact in mind, we will consider its etiology under 4 main headings:

I. Systemic Disorders
II. Drug Toxicity
III. Recognized Acute Glomerular Nephritis
IV. Idiopathic

I. Systemic Disorders

The following conditions will be merely mentioned, as their adequate coverage is beyond the range of this paper.

(1) Intercapillary Glomerulosclerosis occurs in over 40% of long standing cases of Diabetes, and when severe, may produce a Nephrotic Syndrome.

(2) The syndrome is often seen in Renal Amyloidosis which may follow in the wake of Tuberculosis, suppurative conditions and Multiple Myeloma.

(3) Syphilitic nephrosis is a rare occurrence to-day, being suspected chiefly when the syndrome is found in a baby under 1 year of age.

(4) The syndrome may be said to be present in the late toxemias of pregnancy.

(5) Rarer causes are Disseminated Lupus Erythematosis and Renal Vein Thrombosis.

II. Drug Toxicity

Recently, a number of drugs and toxic agents have been shown to cause the Nephrotic Syndrome.

Two cases have been reported following treatment of Petite Mal with Tridione. In both patients symptoms developed insidiously several months after continuous therapy with ordinary dosage levels, and disappeared when the drug was withdrawn. They quickly reappeared in the one patient to whom the drug was readministered. In view of the initially long latent periods, both authors expressed their belief that an immune phenomenon was at fault, rather than any direct toxic action.

Four cases of the syndrome following Poison Oak Dermatitis were reported by Rytand in 1948. Although 3 of the 4

*Adapted from a paper presented before the meeting of A.O.A., February, 1953.

cases had long histories of recurrent dermatitis, no antibodies were demonstrable in vitro to Urushiol, the irritative extract which is common to Poison Oak, Poison Ivy and Sumac. He suggests that this compound is transformed in vivo to a quinone which, in conjugating with renal protein, forms an antigen against which auto-antibodies are produced.

The same author has reported a case secondary to extensive bee stings, and in France, the syndrome has been noted following the therapeutic use of gold salts.

Although Mercury, like the other classical "kidney poisons", produces a tubular necrosis with subsequent anuria, the Nephrotic Syndrome has occurred as an occasional late manifestation of poisoning in children who were receiving standard doses of "worm powders" containing Calomel. In 1952 5 cases were reported in England following prolonged administration of "liver tonics" and "teething powders" containing mercury.

III. Recognized Acute Glomerular Nephritis

We know that the Nephrotic Syndrome may occur at any point during the course of chronic Glomerular Nephritis which was preceded by a recognized attack of acute Glomerular Nephritis. It is currently believed that acute Glomerular Nephritis, which is most common in boys between the ages of 5 and 10, is a disease of reaction to an infection elsewhere. The great majority of the cases follow Hemolytic Streptococcus infections of the upper respiratory tract and occasionally of the skin, but cases have been reported following infections with Strep. viridans, Staphylococcus and Pneumococcus. In this disease, the evidence of a sensitivity reaction is fairly complete, consisting of:

(1) the complete absence of bacteria in the lesion
(2) the 1-2 week latent period
(3) the fall in titre of serum complement
(4) the rise in titre of serum antistreptolysin.

The high antistreptolysin titre seems to implicate streptolysin as the haptene which combines with otherwise non-antigenic renal protein to form a substance against which antibodies are produced. Lange believes that the child's kidney has more antigenic potential than that of the adult—a fact which, if true, would help to explain the higher incidence of acute Glomerular Nephritis in the young. However, the occurrence of the Nephrotic Syndrome under these circumstances is uncommon in the adult, and rare in the child. Indeed, some pediatricians claim that acute Glomerular Nephritis is a benign disease in the child, and only rarely is a factor in the onset of chronic Glomerular Nephritis either in childhood or the adult life of the individual.

IV. Idiopathic

In both children and adults, the situation in which the Nephrotic Syndrome occurs most commonly is one where there has been no history of previous renal disease, no known toxic agents, and none of the recognized diseases which we have considered. Our ignorance of the basic nature of this disease is mirrored by the many times with which it is labelled, a few of the more common being: lipoid nephrosis, subacute nephritis, nephritis type II, and the nephrotic stage of chronic Glomerular Nephritis.

This condition occurs most commonly in children between the ages of 1 and 6, in boys more than girls, and exhibits no

significant seasonal incidence. The more prominent authors seem to be rather equally divided between two views in their conception as to its nature.

(1) Blackman, Bell, Homer Smith et al. consider all cases to represent a nephrotic stage of chronic Glomerular Nephritis in which the acute stage was subclinical.

(2) The other group, which includes Addis, Ellis, Volhard and Fahr, consider it to be a distinct disease entity, and one which is *not* preceded by unrecognized acute Glomerular Nephritis. Controversy as the relationship of this disease to acute Glomerular Nephritis has raged ever since Volhard introduced the concept in 1914.

If we consider the disease as distinct and separate from chronic Glomerular Nephritis, we must then search for new etiologic agents and relationships. Let us consider the evidence—clinical, experimental and pathological.

(1) CLINICAL. Clinically, an analogous relationship to *infection* is not as clearly defined in "lipoid nephrosis" as it is in acute Glomerular Nephritis, but the evidence against such an infection is not conclusive. Hemolytic Streptococci, Staphylococci, and Pneumococci have been suggested. No rise in antibody has been demonstrated to any of these, but Wedgewood and Janeway have found a low complement titre—and whether this is evidence of an immune reaction or of a loss of complement in the urine is unknown. Other evidence is scanty—that for the Pneumococcus consisting of the nephrotic picture which is produced when it is the causative agent in acute Glomerular Nephritis, plus the fact that it is a common cause of death in nephrotic children.

Some have considered the clinical phenomena as secondary evidence of a *metabolic disturbance* of body proteins—caused by toxins, bacterial or otherwise. Epstein has called it "diabetes albuminuricus", and various electrophoretic, immunological and precipitative differences have been noted in the plasma proteins. But much of this work has not been substantiated, and the greater part of it can be more easily explained as secondary to an initial renal lesion.

(2) EXPERIMENTAL. By injecting animals of one species with emulsions of kidneys of a different species, Masocgi in 1900 produced an antibody which was toxic to the glomerulus of the donor species. Later, the basement membrane was found to contain 20x kines as much antigen as the cellular part of the glomerulus. It was noted that the lesion was produced within 24 hours in rats, but not until 1 week in rabbits and dogs, and in these latter species was accompanied by hematuria and hypertension. Many partially successful attempts were made to correlate this experimental lesion with the findings of human "Acute Glomerular Nephritis". However, it was not until 1948 when Heymann and Lund noticed the similarity between lipoid nephrosis in children and the 24 hour reaction in rats, that this work began to pay its well earned dividends. Since then, it has been shown that by merely varying the *dosages* of the same anti-rat kidney serum, one may produce at will clinico-pathological findings strikingly similar to either human lipoid nephrosis or to acute proliferative Glomerular Nephritis. Those animals which survive the immediate degenerative lesion may progress to the proliferative one.

In brief, the reaction to large doses of the serum is one of the swelling and fibrinoid degeneration of the basement membrane within 24 hours. Smaller doses take 7 days to react and produce

typical glomerulonephritic changes of infiltration with polymorphs., endothelial and epithelial proliferation, and splitting of the basement membrane. The reaction in dogs and rabbits is essentially similar to this. Ehrich suggests that an immediate antigen-antibody combination produces the degenerative change, while the proliferative change is caused by the formation of new antibody to the initial antigen-antibody complex.

Therefore the experimental work is indicative of an etiological relationship between lipoid nephrosis and glomerulonephritis, as well as implying that the pathogenesis in each case is different—one being degenerative, the other proliferative.

(3) PATHOLOGICAL. Our consideration of the renal pathology of the Nephrotic Syndrome will exclude those cases due to systemic disease or toxic agent. We will only discuss those cases which, during life, have been diagnosed as either lipoid nephrosis or the nephrotic stage of glomerulonephritis.

The gross picture is identical in both cases—the kidneys being large, pale and soft. The capsule strips easily and on cross-section we notice a widened gray-yellow cortex which contrasts sharply with the brown of the medulla. Radiating yellow streaks are occasionally seen in the cortex, and correspond to fat laden tubules. The medulla, arteries, and the pelvis are not remarkable.

Before passing on to the microscopic picture, we must first consider a few facts concerning the glomerulus. The wall of each glomerular capillary was formerly thought to be a thin, optically structurless basement membrane separating an endothelial and epithelial layer of cells. The functional importance of this basement membrane was stressed by Bell who felt that the cellular layers, especially in childhood, were delicate, sparse, and possibly not intact. Recent work with the newer stains and the electron microscope have shown the basement membrane to be composed of 2 components—an endothelial membrane which is *hyaline* in structure, and is surfaced by a layer of *mucoid* material elaborated by the epithelial cells. It is thought that the structural changes to be described take place in the hyaline endothelial membrane.

In Fahr's classical description of the pathology of lipoid nephrosis in 1914, the stains in use were so inadequate that the glomerular changes were passed off as consisting only of some swelling of the endothelial cells and occasional adhesions to the capsule. Thus arose the concept of a "pure lipoid nephrosis" with only tubular pathology. In describing his Nephritis II, Ellis in 1942 noted occasional thickening of the basement membrane but it remained for Bell in 1948, using a trichrome stain, to demonstrate that this irregular thickening was almost a constant finding in those over 12 years of age with lipoid nephrosis, and was a frequent finding in those under 12. In only 18 of his 55 cases did the basement membrane appear normal, and of these, 15 were under 10 years of age. Since then, Allan, Ehrich and others, using recently developed tissue stains, have demonstrated thickening and fibrinoid degeneration of the basement membrane in nearly every case which presents the nephrotic syndrome.

The findings described of "pure lipoid nephrosis" are found commonly in children but only rarely in adults, where nearly all cases show the associated glomerulonephritic changes of epithelial and endothelial proliferation. It is the marked epithelial or extracapillary proliferation that produces the well-known epithelial crescents of glomerulonephritis

which were formerly thought to be diagnostic of:

—the subchronic stage of Volhard
—the degenerative stage of Addis
—the nephritis, type II of Ellis, and the
—"*mixed* lipoid nephrosis" of other authors.

These proliferative changes are associated with a splitting and laminating of the basement membrane as well as a thickening.

We now realize that either of these characteristic lesions may progress to the stage of glomerular ischemia and consequent chronic hyalinizing glomerulonephritis.

The tubular pathology is the same in both conditions and so outstanding that Munk coined the term "lipoid nephrosis", believing that it was evidence of primary degeneration rather than secondary to the glomerular lesion as is now believed. The changes, found throughout the entire tubule, are maximal in the proximal segment. Here there is an irregular deposition of partly birefrigent lipoid causing the epithelial cells to appear swollen and distorted. Associated changes are colloid droplets and mild focal atrophy along with a few pyknotic nuclei. The lumen may contain occasional xanthomatous cells and rarely a mild focal infiltration with lymphocytes. The arteries are not remarkable.

The most logical explanation of this fatty change in the tubular cells is that it is evidence of damage caused by the excessive absorption of protein molecules from the glomerular filtrate. It is a reversible change and produces very little derangement of function.

Summary

In summary, we find that in spite of much speculation and many theories, the etiology of many cases of the nephrotic syndrome remains obscure. The clinical investigations indicate that a search for toxic agents, systemic disease, and previous infection should always be made. The observation that the nephrotic syndrome as well as acute glomerular nephritis may be produced experimentally by the same procedure suggests that the human counterparts may be etiologically related. The pathological investigations indicate that two distinct patterns of glomerular disease may be found—one which corresponds to the "pure nephrosis" described by earlier pathologists but which is now more uniformly revealed by new staining techniques—and one which shows varying degrees of glomerulonephritic changes. Both may cause the nephrotic syndrome. Both may progress to renal insufficiency.

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REFERENCES

1. Addis, T.: Glomerular Nephritis, Macmillan, 1948.
2. Allen, A. C.: The Kidney. Grune & Stratton, 1951.
3. Barnett et al.: Adv. in Pediatrics, Year Book Publishers, 1952.
4. Bell, E. T.: Renal Diseases, Lea & Fibiger, 1947.
5. Blackman, S. S.: Bull. John Hopkins Hosp. **57**:70, 1935.
6. Ellis, A.: Lancet **1**:1, 42.
7. Elwyn: Nephritis, Macmillan, 1929.
8. Greenspon & Krakower: Fed. Proc. **10**:355, 1951.
9. Heymann & Lund: Pediatrics **7**:69, 1951.
10. Smith: The Kidney, Oxford Univ. Press, 1951.
11. Van Slyke: Observations on Bright's Disease, Williams, 1930.
12. White: J.A.M.A. **10**:376, 1948.
13. Wilson et al.: BMJ. 350, 1952.
14. Ehrich et al.: A.M.H. Archives of Pathol. 52.

WOMEN PIONEERS IN ENGLISH MEDICINE

W. F. G. RICHARDSON, M.B., B.S.(Lond.)

We are wrong to think that women have been practising medicine only during the last century. Throughout the ages there are stories of women physicians and surgeons. At times of war women were expected to heal the wounded men and to cure the sick at home. It was an important part of the work of abbesses and nuns in convents to care for the sick. Part of the duty of a housewife in the 17th Century was to have knowledge of herbs so that she could make medicines for her family and neighbours. (In fact the housewives of that time seem to have been expected to do almost as much as we modern women.) There are also, of course, stories of hostility towards women physicians. Especially between wars, men had time to become alarmed at the success the women were achieving. The Guild of English Surgeons in 1541 resolved that "No carpenter, smith, weaver or woman practise surgery". On the whole, however, in the days when the art of Medicine included a certain amount of magic, women practised it along with men. As the study became more scientific, the standard of medicine gradually rose and the women were excluded, chiefly because there were not the educational facilities for them. Also, they were up against a widespread opinion that the female brain was smaller and lighter than the male and, therefore, incapable of such scientific study. Besides all that it was considered that women should keep their feminine qualities and not be exposed to indelicate sights. During this past century the struggle of women in medicine has been part of the general movement for their emancipation. It is interesting to consider the sort of life they led at the beginning of Queen Victoria's reign. (Incidentally Queen Victoria did not like the idea of women's emancipation and as the movement grew she liked it less and less.)

As a result of the industrial revolution, large scaled mechanised industry took the place of small individual businesses. Working class girls were employed in the factories but amongst the middle class it was a sign of gentility to be idle. "A milk-white lamb that bleats for man's protection". That line of Keats aptly describes a girl considered ideal in that day. She was allowed to do embroidery or collect shells or sing a little but her first duty was to please the opposite sex. It was considered a disgrace not to marry but any money a wife earned, or was given, became the property of her husband and she could not use it without his consent. The gentlewoman who had to maintain herself was to be pitied the most because the only paid occupation open to her was that of a governess under despised conditions and at a miserable salary. Obviously the only solution was for women to become better educated. Some intelligent, energetic young women formed themselves into the Langham Place group. They published a newspaper, *The Englishwoman's Journal*, and they started a Society for Women's Employment. The early attempts to find

suitable occupation for girls were discouraging. When it was suggested to an hairdresser that women might be employed in his trade he said, "Impossible. I myself took a fortnight to learn it". Amongst the lectures arranged by the Langham Place group were three given by Dr. Elizabeth Blackwell. Her subject was "Medicine as a Profession for Ladies". Dr. Blackwell was born in Bristol, England, and emigrated to the U.S.A. with her family when she was a child. After many difficulties, including finding a medical school that would accept a female student, she graduated from the University of Geneva, N.Y., in 1849 at the age of 28. Her fame spread through stories in the Press and the following is the salute to her in *Punch*:

"Young ladies all of every clime,
Especially of Britain,
Who wholly occupy your time
In novels or in knitting,
Whose highest skill is but to play,
Sing, dance, or French to clack well,
Reflect on the example, pray,
Of excellent Miss Blackwell.

Think if you had a brother ill,
A husband or a lover,
And could prescribe the draught or pill
Whereby he might recover;
How much more useful would this be,
Oh, sister, wife or daughter!
Than merely handing him beef tea,
Gruel, or toast and water.

Ye bachelors about to wed
In youth's unthinking heydey,
Who look upon a furnished head
As horrid for a lady,
Who'd call a female doctor 'blue',
You'd spare your sheers, brother
Think, my young fellows, if you knew
What physic costs a father!"

Ten years later it was comparatively easy for women to get medical training in America. Elizabeth Blackwell, therefore, went to visit England to help the women's cause. While she lectured she noted in the audience a "bright, intelligent young lady". This was Elizabeth Garrett who was then aged 23 and felt free of obligations at home and wanted to pursue her wish to find some suitable occupation. She had already been urged to take up medicine by Miss Emily Davies who was later the founder of Girton, the well known women's college at Cambridge. At first Mr. Garrett tried to dissuade his daughter but soon he became her staunchest ally. In 1860 she started at the Middlesex Hospital and the year spent there was the best and most consecutive part of her training. At first she worked as a nurse and later attended some lectures and demonstrations and was allowed to dissect but was never accepted as a student. She had to leave at the end of a year because the lecturers disliked the presence of a woman although they held her in high esteem personally. A majority of the students also voted for her dismissal. Surprisingly, however, she secured a promise from the Society of Apothecaries that they would examine her for the Licence to practise if she served a five year apprenticeship with a qualified medical practitioner and received instruction from recognized university tutors. Besides a licence, she wanted a university degree. None of the universities in the British Isles allowed women to matriculate. Some of you, still fresh from the strain of that exam, might momentarily envy the women of that day but you will soon realise it meant no women could attend university. After short, unsuccessful attempts to study at St. Andrew's University and the London Hospital,

Elizabeth Garrett settled down to serve her apprenticeship and obtain the required certificates by private tuition. In 1865 she passed the examination of the Society of Apothecaries and obtained the licence to practise. They were unable to prevent this but in order to avert the disaster of any more women applying to take the examination, they made the rule that candidates must have worked in a recognized medical school. Thus for a further 12 years there were only two women's names on the British Medical register—those of Elizabeth Blackwell and Elizabeth Garrett. The latter immediately started to practise and soon opened a clinic which eventually grew into the hospital named after her. When Paris University opened its medical degrees to women she re-studied French and took the M.D. there. She was elected to the first London School Board and was appointed to the staff of a children's hospital where she met Mr. Anderson—a London ship-owner and a member of the Hospital Board. They were married in 1871 and she then showed it was possible to be an efficient physician, wife and mother. She also found time for reading, concerts and entertaining. It was while she was busy with her practice and young family that another pioneer, Miss Sophia Jex Blake, took the lead in founding the London School of Medicine for Women. The two had known each other for years but unfortunately were incompatible in temperament. They admired each other to a degree and had in common the aim to help other women to wider opportunities and it is interesting to compare their different methods. Elizabeth Garrett Anderson believed in peaceful persistence whereas Sophia Jex Blake was impetuous and believed in frontal attack. Sophia Jex Blake had not thought of medicine as a career until at the age of 29 she was in the States and was influenced by Elizabeth Blackwell and her disciples. Returning to Britain, she fought until she obtained permision for women to enter Edinburgh University as medical students. Five women matriculated and all went well for six months. Then the storm broke, chiefly because a woman had the effrontery to lead the class in Chemistry. The professor, however, awarded the coveted scholarship to the man next on the list. The women did not contest it but the unfairness attracted wide-spread attention. The University was criticised by the medical and lay press and the women lost much of the goodwill amongst the medical faculty, some of whom determined that the women be driven from their university. The battle continued for three years and it was not only verbal but at times the women were pelted with mud and rotten eggs. Although they had the support of some of the most influential men in Edinburgh and could take some courses, they were unable to obtain full clinical instruction and were not allowed to get a degree. Finally in 1873 the women had to leave Edinburgh University. They were again rejected by the Universities of St. Andrews, Durham and London, and the two recognized London medical schools refused to admit them as students, so Sophia Jex Blake and her advisers formed the idea of the London School of Medicine for Women. Within three months she had found and leased a house and had it ready for 14 students to start their training (in Oct. 1874). As teachers they were able to get men who were on the staff of recognized medical schools and who wanted to help the women. Two years later in 1876 it was feared the school would have to

close because of two serious difficulties—first, no hospital would admit them to obtain clinical experience and second, no board of examiners would examine them. The women persevered and the turning point in the campaign came when after a long debate the General Medical Council gave the guarded decision that they were not prepared to say that women ought to be excluded from the profession. This led Parliament to pass an Act giving all British Medical Boards the right to admit women for examination. Of course, this did not mean that all Boards were *compelled* to do so but the Irish College of Physicians immediately recognized the London School of Medicine for Women and in 1877 examined and awarded their M.D. to the 5 women who had started their course in Edinburgh. That same year the School Committee was finally successful in persuading the Board of the Royal Free Hospital to allow the women students to get their clinical instruction there. Thus the school was fully established and it was Sophia Jex Blake who made the greatest contribution. While fully recognizing this, the Governing Body did not consider her the right person to be the first official Secretary to the school—a position requiring more patience and tact than she had. Disappointed, she went to Edinburgh to practise and later started there an hospital and a school of medicine for women. She remained a Trustee of the London school for 20 years and then resigned chiefly because of her antagonism to Elizabeth Garrett Anderson. The latter was appointed Dean in 1883 and showed good organizing ability. During the 20 years she held office the number of students increased from 40 to 318, the school was rebuilt on the old site and the hospital was enlarged. In 1901 the school became a recognized medical college of the University of London which had admitted women students to all faculties in 1878 and from then on was friendly to the women's cause.

By the beginning of the 20th Century women could study medicine in many places and the next step was to find ways of increasing their chances to get postgraduate experience. Partly in order to overcome this problem, and partly because many women preferred to be treated by one of their own sex, a number of hospitals staffed entirely by women were started. One of the best known of these is EGA in Euston Rd. In 1944 the Report of a Committee headed by Sir William Goodenough recommended that Exchequer Grants be given to medical schools only if they were co-educational. Hence women are now admitted as students to all the London medical schools. Their opportunities to get better postgraduate experience have also been increased by the same Report's recommendation that "all hospital appointments are filled by open competition and that the sex of the applicant is not a bar to appointment."

And so we come to the present with the field of medicine so large that there is scope for many aptitudes. It is not as necessary, now, for a woman to be exceptionally brilliant or to struggle exceptionally in order to qualify as a doctor. Her place in medicine and in its institutions is established. A moment in the present, it has been said, is the sum of the past. To realize this is at once to acknowledge our debt to the past and our obligation to the future.

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EDITORIAL

AWARD WINNER AGAIN

C.A.M.S.I. has recently announced that the Charles E. Frosst trophy for the best undergraduate Medical Journal in Canada has been awarded to the University of Toronto Medical Journal, Volume XXX. This is the third time, in the four years that the trophy has been offered, that it has been won by the JOURNAL. Without the enthusiastic support which the JOURNAL has received from the Medical Society and the student body of this Faculty such an honor would have been impossible.

Volume XXX was the result of the many hours of work devoted to it by its staff and its success is due to their untiring efforts which were so ably directed by Dr. W. E. Sullivan. The presence of the Frosst trophy in the Medical Reading Room again this year will serve as a constant reminder to us of their achievement.

GASTRIC ANTACIDS*

J. K. W. FERGUSON, M.B.E., M.A., M.D., F.R.S.C.

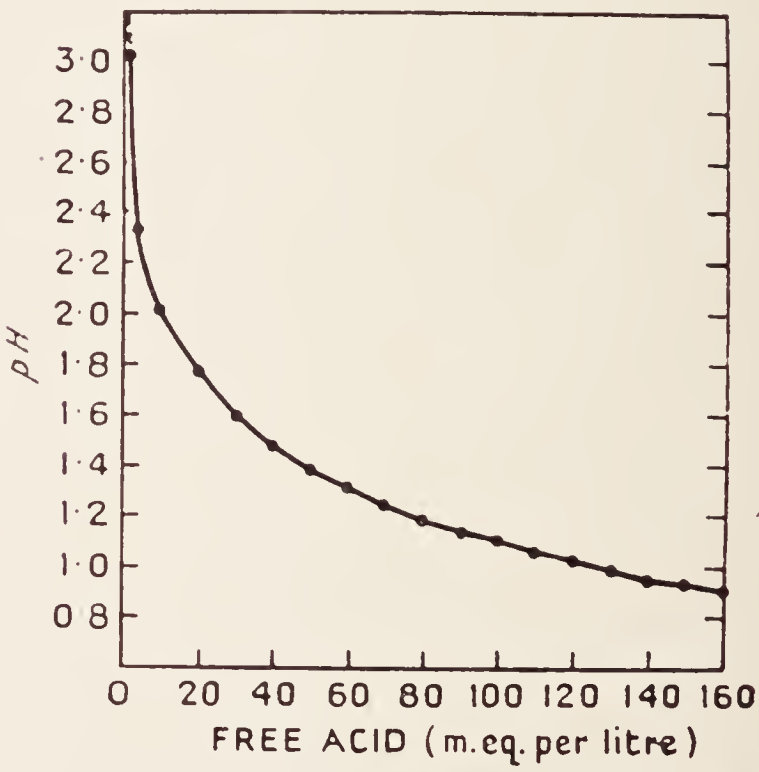
Gastric antacids comprise a large number of drugs which are used to "neutralize" the acidity of gastric juices. Some authors include under the same title drugs which reduce the secretion of gastric juice. It is better, however, to call the latter anti-secretory drugs. This article will deal only with drugs used to neutralize gastric juice.

A question which must be dealt with early is, what constitutes adequate neutralization? A satisfactory answer must also answer the question, adequate for what?

Two systems of terminology are used to describe the acidity of gastric contents, (1) the pH scale, (2) the clinical scale of titratable acidity.

Fig. (1) shows the connection between the two scales. The "clinical units" of acidity have the same meaning as milli-equivalents of acid per litre. Free acidity is determined by measuring the number of cc. of 0.01 N NaOH required to raise the pH of 10 cc. of strained gastric contents to the point where an indicator (Töpfers reagent) changes colour, i.e. to a pH of about 3.5. At pH values below 2.0 the titratable free acidity is a much more sensitive scale of acidity than is pH. Above pH 2.0 the pH scale is more sensitive than the titration scale, i.e. intervals which are easily measured on the pH scale are scarcely measurable by titration.

The optimum pH for the action of pepsin is said to lie between pH 1.5 and pH 2.2. The corresponding titratable free acidities are 40 and 5 units respectively. As the pH increases above 2.2 the activity of pepsin decreases rapidly. Its activity is said to be almost zero at pH 5. Kirsner and Palmer and their associates (1) state that "effective neutralization may be defined as maintenance of the pH (of gastric contents) between 4.0 and 5.5 or



Relation between pH and titratable free acid.

higher since at this hydrogen ion concentration the free acid and peptic activity are eliminated." These authors have in mind the use of gastric antacids as adjuncts in the serious therapy of peptic ulceration. In this light their statement seems reasonable. A number of antacid drugs which enjoy substantial sales, namely many aluminum hydroxide gels, seldom raise the gastric pH even as high

*Department of Pharmacology, University of Toronto.

as 3.5. But there is no reason to doubt that they can give symptomatic relief.

It is important to realize that the greatest use, in terms of volume, of gastric antacid drugs is not for the intensive therapy of peptic ulcer. It is probable that the great bulk of antacid therapy is self-administered without the benefit of medical advice, for intermittent or more or less temporary "indigestion". There is little doubt that the patient usually obtains, with relatively small doses of the antacid of his choice, satisfactory relief from his symptoms, and seldom has to bother a doctor about them.

One may infer that symptomatic relief is often obtained at levels of pH far below 3.5 and perhaps even below 2.0. It would be interesting to know what degrees of acidity may give rise to the discomfort which so many people describe as "acid indigestion". The question has not been studied in this form but certain conclusions may be drawn from the large number of investigations which have been made on the role of acidity in the production of pain in gastric and duodenal ulcer. Alvarez (2) ably summarizes the confusing story and concludes that acid must be an important factor in the production of pain in many cases of peptic ulcer. This conclusion is in no way invalidated by the fact that some persons with and without ulcer, experience no discomfort when 300 cc. of 0.1 N HCl (pH 1.08) are instilled into their stomach. It has often been observed that a patient with ulcer may react one day with severe pain to the instillation of 0.1 N HCl and on another day feel no discomfort. These differences from day to day in sensitivity to acid are attributed to changes in the state of irritation or inflammation of the gastric mucous membranes at or around the site of the ulcer.

It has been amply demonstrated that some persons with or without ulcer, are remarkably insensitive to acid in the stomach. On the other hand, some persons, in apparent good health, experience decided discomfort if they swallow solutions with a pH not lower than 2.5. The discomfort is relieved by antacids in small doses.

It seems that the threshold acidity for the perception of acid irritation in the stomach varies greatly in different persons, and in the same person from time to time. In some persons symptoms may be aroused by minor degrees of hyperacidity and relieved by small doses of antacid. In other persons a high degree of acidity may be required to cause symptoms of irritation. In such cases a slight reduction of the acidity may be sufficient to relieve the symptoms. If such a person has a peptic ulcer, large doses of antacid may be required at frequent intervals to secure adequate neutralization, for the protection of the ulcer. If the ulcer gets worse, the patient's sensitivity to acid may increase and it may become necessary for him to take large doses of antacid to secure relief from pain, whereas small doses were previously sufficient.

The answers to the questions in the second paragraph seem to be: (1) For the relief of discomfort of temporary "acid indigestion" it may not be necessary to raise the gastric pH above 2.0 and small doses of almost any gastric antacid may suffice. (2) For serious therapy aimed at protecting a peptic ulcer from peptic digestion, one should probably aim for a gastric pH of 4.0 or higher for long periods in each day. To achieve such levels the more alkaline antacids, e.g. combinations of calcium carbonate and magnesium carbonate, are necessary.

In discussing the treatment of peptic ulcer, physicians tend to divide themselves into two schools, (1) those who follow the teachings of the late Dr. Sippy and stress the importance of neutralizing gastric acidity, (2) those who minimize the importance of antacid therapy and stress the importance of all the other factors which may influence the course of the disease, viz. a regular daily routine of meals and rest and relief from worry. The cleavage between the two schools of thought is probably less in practice than in verbal expression. In any case, it is not the function of this article to discuss the merits of these schools of thought but to discuss the characteristics of antacids in action.

Antacids differ greatly in three important and independent characteristics, (1) alkalinity, (2) acid combining power, and (3) speed of reaction. No standard method of measuring or expressing these characteristics has gained general acceptance. Each author or investigator has invented his own method of measurement which differs in detail from that of others. (3, 4, 5, 6, 7) It is not surprising that some confusion and misunderstanding has occurred. In principle each of these three characteristics can be evaluated and described by means of experiments *in vitro*. Other important characteristics must be evaluated *in vivo* and eventually in human patients. Such characteristics include (1) constipating or laxative action, (2) systemic effects on acid-base and electrolyte balance, (3) stimulant or depressant effects on gastric secretion.

Acid Rebound

Some antacids, notably sodium bicarbonate, have been accused of causing "acid rebound". The phrase is often used without adequate definition and some authors seem to mean by this expression merely a short duration of action with a rapid return of hyperacidity. Others seem to infer that sodium bicarbonate causes an increased secretion of hydrochloric acid. Others again infer that increasing the pH of gastric contents much above pH 7 may cause a secretion of hydrochloric acid. There seems to be little justification for this last inference because one of the most alkaline of gastric antacids, magnesium oxide, seems not to have any secretory action. Lockwood and Chamberlin (8) who thought that they demonstrated "acid rebound" with sodium bicarbonate felt that their experiments exonerated magnesium oxide.

The idea that sodium bicarbonate may increase the secretion of hydrochloric acid has received support from experiments on dogs (9) and frogs (10). The implications are interesting but a re-examination of the reports of numerous experiments on humans with the doses used in therapy lead one to believe that the importance of "acid rebound" as a consequence of taking sodium bicarbonate has been greatly exaggerated.

Under experimental conditions in dogs it has been shown (9) that sodium bicarbonate in the stomach increases the amount of hydrochloric acid secreted as a result of injections of histamine. The explanation for this effect was not clear. It was thought by some authors that CO_2 liberated by the action of HCl on sodium bicarbonate might stimulate the gastric mucosa causing the secretion of acid. Other investigators felt that an increased level of bicarbonate in the blood was in some way responsible for this increased production of acid. It is possible now to reconcile these rather vague and incon-

sistent ideas but before doing so, let us dispose of the question whether sodium bicarbonate in the doses given to human patients does or does not cause any significant increase in the secretion of hydrochloric acid. A re-examination of the many experiments which have been done on human patients with peptic ulcer lead me to the conclusion that none of them ever demonstrated "acid rebound" after bicarbonate, in the sense of an increased secretion of acid. The idea of acid rebound was, however, so widely accepted that a prominent gastro-enterologist once said that sodium bicarbonate is one of the best known stimulants of gastric secretion. The history of this erroneous opinion originated with clinical experiments at a time when techniques for evaluating and discounting variations in human reactions were not well known. The idea seemed to be supported by animal experiments. It seemed reasonable. As a consequence sodium bicarbonate was given a very bad name as an antacid—a bad name which was sedulously emphasized by the promotors of rival products. Sodium bicarbonate has some unfavourable characteristics which will be mentioned later but at this point let us consider the evidence which led Davies and Longmuir (10) to conclude recently that an ideal gastric antacid should be capable of liberating CO_2.

BICARBONATE AND THE SECRETION OF HCL

The story is briefly this. Hydrochloric acid is produced in the oxyntic cells of the gastric mucosa, presumably from sodium chloride. When the HCl enters the lumen of the stomach, sodium ions remain behind in the cells. They are neutralized by bicarbonate ions which come from CO_2 produced in the cells. During active secretion of HCl the CO_2 produced locally in the secreting cells is not sufficient to supply the required amount of bicarbonate. Additional CO_2 must come from the blood. If the CO_2 content of the blood is low, as in acidosis which is a state of diminished alkali reserve, the production of hydrochloric acid will be hampered. If the mucosa of the stomach is bathed with bicarbonate solution, this solution can serve as a source of CO_2 which can sustain the process of secretion of hydrochloric acid. Now we have an explanation of the older experiments on dogs which seemed to show that bicarbonate in the stomach or in the blood could increase the secretion of hydrochloric acid by the gastric mucosa. It probably does so only if the production of HCl is limited by a lack of available CO_2 at the time.

PROTECTIVE ACTION OF CO_2

Davies and Longmuir went on to show in the frog that ulceration of the gastric mucosa occurred if the secretion of HCl was forced by histamine in spite of inadequate supplies of CO_2. They postulated that if a sufficient supply of bicarbonate ions was not available the excess of sodium ions formed NaOH, which had a destructive action on the cells, leading to multiple ulceration. This was their reason for suggesting that the ideal antacid should be capable of releasing CO_2. It seems to me that one may appreciate their ingenious experiments and hypothesis without necessarily agreeing with their clinical advice. It seems unlikely that gastric ulceration in the human occurs as a result of a local shortage of CO_2. But the idea may be worth keeping in mind. A similar process may be of importance in duodenal ulceration. The duodenal cells secrete an

alkaline juice containing sodium bicarbonate. Presumably they do so by transferring HCl into the blood. The sodium ions remain in the cells and combine with bicarbonate ions derived from CO_2 produced locally or transferred from the blood. Here, again, a shortage of CO_2 could result in unneutralized sodium ions forming NaOH with caustic consequences. The evidence for the idea is provided by experiments by Cummins, Grossman and Ivy (11) who found that duodenal ulcers could be produced in dogs by the continuous infusion of hydrochloric acid into the stomach, but only if the dogs were permitted to develop acidosis. If acidosis was prevented by the intravenous infusion of sodium bicarbonate no ulcers appeared. Obviously we have some new evidence to consider in relation to the pathogenesis of gastrointestinal ulcer.

Disadvantages of $NaHCO_3$

Sodium bicarbonate has now been largely cleared of charges of causing "acid rebound". It has been accorded the potential virtue of protecting the mucosa from ulceration. It has long been known as a fast acting antacid which gives gratifying symptomatic relief. It is only fair to list some of its handicaps. The most important is the ease of absorption of the sodium ion and consequent possibility of producing a systemic alkalosis. Another disadvantage, which is due to the solubility of the drug, is its rapid evacuation from the stomach and consequent short duration of action. The liberation of CO_2 from sodium bicarbonate, or calcium or magnesium carbonate, may be dangerous in one special circumstance, namely, poisoning by the ingestion of strong acid. In such cases it is possible that an excessive production of CO_2 might produce acute dilatation of the stomach or even perforation. It would be safer to use an antacid which liberates no CO_2, e.g. milk of magnesia, or aluminum hydroxide, or milk.

Secretory Action of Milk

Experiments *in vitro* show that milk is a very effective antacid which is capable of neutralizing large amounts of acid very rapidly (see Table I). Its efficiency in the stomach, against HCl produced by the stomach, is very much less. The reason, of course, is that milk is a protein food which stimulates the secretion of gastric juice, not excessively but sufficiently to secure its own digestion. Kirsner and Palmer (12) have shown that milk alone, or milk and cream, given every hour keep the pH of gastric contents between 1 and 2, no higher. To raise the pH to 4 or 5 it is necessary to add other antacids, such as calcium carbonate.

Duration of Action

In all clinical investigations on antacids one conclusion is sustained unanimously. The duration of action of all of them is short, viz one hour, or at the most an hour and a half. In patients with peptic ulcer receiving a soft or liquid diet, the shorter duration of action is more typical (13). The so-called long-lasting antacids (which means the relatively insoluble ones) sometimes give an illusion of prolonged action, particularly if samples of gastric juice are taken from the body of the stomach rather than the pyloric antrum. The heavier granules of insoluble antacid can settle to the bottom of the body of the stomach. Gastric juice can flow around the particles of food and antacid and pass through the pylorus and into the duodenum quite unneutral-

ized. If gastric contents are taken from the fundus, particles of solid antacid may be aspirated into the sample and dissolve in it before measurements of acidity are made (14, 15) thus giving a high pH which does not represent the pH of the juice entering the duodenum.

Doctors who use intensive antacid therapy have found it necessary to give large doses every hour, e.g. up to 4 Gm. of $CaCO_3$ every hour during the waking hours. On such a regimen it is not possible to neutralize the acid secreted during the night, although the nocturnal secretion may be very copious. At the present time experimentation is proceeding with various antisecretory drugs such as methentheline (Banthine), atropine and hexamethonium. There is some evidence that they can prolong the emptying time of the stomach, decrease secretion and in both these ways prolong the action of antacids and so make a single dose given at bed time effective for a longer time (14). It must be admitted, however, that none of the methods mentioned so far is entirely effective in controlling nocturnal hyperacidity.

CONTINUOUS INTRAGASTRIC DRIP

Continuous intragastric drip was introduced by Winkelstein in 1932 (16) in order to achieve control of gastric hyperacidity in ulcer patients for 24 hours of the day. A tube was introduced into the stomach through the mouth or nose and left in place for days or weeks at a time. Through the tube the patient was given by continuous drip 3 quarts of milk each day. To each quart was added 5 Gm. of sodium bicarbonate. Some years later aluminum hydroxide gel, or aluminum phosphate gel, was used instead of the sodium bicarbonate (17). The Winkelstein drip has been widely used throughout the world, in spite of its rather obvious disadvantages. Needless to say, it is not used on all cases of peptic ulcer but is reserved for the more refractory ones.

THE ANTACID LOZENGE

The principle of continuous drip was applied in a novel manner by Douthwaite and Batty Shaw (18). They devised an antacid lozenge consisting mostly of milk powder and magnesium oxide. When held in the cheek, it dissolved slowly in about 20 minutes. During this time the acidity of the gastric contents in the pyloric antrum was entirely neutralized. Obviously this mode of continuous administration of antacid is not applicable during hours of sleep. Perhaps, too, one might become tired of sucking lozenges for sixteen hours a day. This much seems clear—longer periods of effective neutrality can be maintained by the slow oral intake of a suitable antacid lozenge, with much smaller total intake of alkali than is possible even with hourly doses which are swallowed at once. One is reminded of the old concept of the stomach pathway—the magenstrasse. According to Waldeyer (2) the lesser curvature of the stomach (the magenstrasse) acts like a gutter or drain which guides swallowed fluids directly from the cardiac sphincter to the pyloric antrum. The rapid effect of the slowly swallowed antacid and the abruptness with which the action ceases when the lozenge has all been swallowed, support the idea of direct passage from the oesophagus to the pyloric antrum. The old hypothesis of the magenstrasse provides a plausible explanation for the very efficient action of these antacid lozenges, or M tablets as they were called by

Douthwaite. Lozenges of this type are sold under the trade-marked names, Milkali (B.D.H.) and Nulactin (Horlick).

Choice of Antacid

Table I shows a list of the more popular antacid drugs. Each drug alone or in combination with others has enjoyed a measure of popularity. Each is capable of inducing a gratifying degree of relief from symptoms due to hyperacidity. Each can be used effectively for symptomatic therapy if its characteristics are understood. For intensive and prolonged antacid therapy a choice should be made from a narrower range of products.

The most important characteristics to be kept in mind are:—(1) laxative action, (2) constipating action, (3) systemic actions, particularly the capacity to induce alkalosis, (4) acid combining power.

The magnesium salts are all laxative except magnesium trisilicate, which has little effect on most patients. The calcium

TABLE I

Acid Combining Power of Various Antacids

Antacids	Dose Gm. or cc.	Acid Equivalents cc. N/10 HCl A Theoret.	B Actual*	B/A
$Al(OH)_3$ gel (6%)	10	240	110	0.46
T.N. Amphojel, Creamalin				
$Al(OH)_3$ gel (dried)	0.5	200	65, 27	0.32
Amphojel tablets				
$AlPO_4$ gel (4%)	20	110	(slow)	
Phosphojel				
$Al(OH)_2$ glycinate	0.5	175	130	0.75
Alglyn, Aspogen				
$CaCO_3$	1.0	210	175	0.83
Precipitated Chalk				
$Ca_3(PO_4)_2$	1.0	190	74	0.40
Tribasic CaPhos.				
$CaHPO_4$	1.0	115		
Diabasic CaPhos.				
MgO	0.5	250	220	0.88
MgOH (tabs.)	0.5	170		
Magnesia Magma (8%)	10	270	245	0.90
Cream of Magnesia				
T.N. Milk of Magnesia				
$MgCO_3$	1.0	200	150 (?)	0.75
$Mg_3(PO_4)_2.5H_2O$	1.0	170	115	0.68
$2MgO.3SiO_2nH_2O$	1.0	150	92	0.62
Mg. Trisilicate				
Polyamine-Methylene Resin	1.0	100	50	0.50
Resinat, Exorbin				
$NaHCO_3$	1.0	120	118	0.98
Milk	200		180	(fast)
Mucin	1.0	15		

*To pH 3.5 in 10 min.

In the last column, figures over 0.75 indicate relatively fast neutralizing action. These representative figures have been compiled from various sources (3, 4, 5, 6, 7).

salts are constipating. By combining calcium salts with the laxative magnesium salts in approximately equal molecular proportions, e.g. equal parts by weight of magnesium carbonate and calcium carbonate, a combination is obtained which has little or no effect on the bowel movements of the average person. The proportions may be varied by trial to suit the needs of patients with a tendency to constipation or laxation. The aluminum hydroxide or phosphate gels are constipating for some patients. The so-called "non-reactive" aluminum hydroxide gels are said to have little constipating action but they also have a low acid combining power (19). A combination of aluminum hydroxide gel, 4 parts by volume, with milk of magnesia, 1 part by volume, is recommended by some authors (20).

The tendency to produce systemic alkalosis is always quoted as a disadvantage of sodium bicarbonate. Alkalosis seldom occurs, even with large daily doses such as 15 Gm. a day, unless the patient is vomiting or losing large amounts of chloride and water by the aspiration of stomach contents (1). Nevertheless, the possibility of alkalosis exists and had led to the adoption of the relatively non-absorbable (or non-systemic) antacids in preference to sodium bicarbonate for intensive antacid therapy.

The acid combining power of antacids per unit weight or unit volume varies greatly and determines the dose which should be given to obtain comparable effects. Note in particular the difference between aluminum hydroxide gel and aluminum phosphate gel as shown in Table I.

Acid combining power is an expression which requires some explanation. For the insoluble antacids a time limit is necessary and for all drugs an end point must be specified, i.e. a minimum pH which may be regarded as effective neutralization. As an illustration we may cite the specifications prescribed by the U.S.P. for aluminum hydroxide gel. The gel is exposed to an excess of acid and shaken continuously for one hour at a temperature of 37°C. The filtrate is separated from sediment and excess acid is titrated with sodium hydroxide to an end point with brom-phenol blue as an indicator. The end point is pH 3.0-3.5. The conditions of continuous shaking and substantial excess of acid mean that the aluminum hydroxide preparation may perform to better advantage in the test than in the stomach. The time limit of 10 minutes with agitation, as stated in Table I, probably gives a better picture of what to expect in the stomach. The stomach is not a churn! It behaves much more like a hopper. The U.S.P. requires that each Gm. of aluminum hydroxide gel shall combine with not less than 12.5 and not more than 25 cc. of N/10 HCl. Within these rather generous limits it is fair to say that the required acid combining power corresponds roughly to the theoretical combining power shown in Table I. It is evidently possible to obtain samples of aluminum hydroxide which do not combine readily with N/10 HCl. The same is true of magnesium trisilicate.

RESINS

Synthetic resins of a type used as water softeners have been purified for use as gastric antacids. The ones most commonly used are polyamine resins which are sold under the names Exorbin, Resinat, and Kambion. The resin molecule contains large numbers of substituted amino groups ($\equiv$N). At acid pH

the amino groups combine with HCl to form $\equiv NH^+ Cl^-$. In the intestine, where the pH is higher, $-\underset{|}{N}-HCl$ reacts with sodium bicarbonate to form NaCl. The resin is excreted by the bowel in its original form. The resins are practically insoluble, are not absorbed, and are designed so that they do not affect the electrolyte or acid base equilibrium. They also inactivate pepsin to some extent by adsorption. In short, they have the properties of an ideal antacid but their acid combining power is rather weak in relation to their bulk and they are still expensive.

MYTHS AND RED HERRINGS

The word "adsorption" is often invoked to explain the action of the less soluble antacids, magnesium trisilicate, aluminum hydroxide, and the resins. What is usually meant is simple combination of hydrochloric acid with a basic molecule or radicle which remains insoluble, e.g. an NH_2-group on a resin or with half the valence of a magnesium atom which remains attached to silica by the remaining valence. There is no fundamental difference between such reactions and reactions between acids and bases in solution. Technically such reactions may be called adsorption because they are chemical reactions at surfaces. It seems better, however, to reserve the term adsorption for the less well defined reactions whereby finely divided particles of solid, e.g. aluminum hydroxide, calcium carbonate, and magnesium trisilicate, may combine with proteins like pepsin, and with other complex organic chemicals by means of van der Waal's valences or polar forces. Such reactions may play a part in antacid therapy by inhibiting peptic action but it is hard to assess their importance.

A rumour has been circulated that aluminum hydroxide is dangerous to give to patients with a bleeding ulcer. It is said that aluminum hydroxide combines with blood to form a gummy mass which may obstruct the small intestine. As far as I can tell, such a reaction does not occur *in vitro* and must be very uncommon in patients. The story seems to have originated with one patient admitted with a bleeding duodenal ulcer, and who developed fatal intestinal obstruction several days later. The patient was given aluminum hydroxide by continuous intragastric drip, feedings of gelatin water and gruel, and what may be the really important factor, morphine sulphate every four hours for several days (21). It seems likely that dehydration and the morphine were jointly responsible for the inspissated gummy mass of aluminum hydroxide which caused the obstruction.

Summary

If the symptoms of temporary indigestion are relieved by small doses of antacid, the choice of antacid is of no great importance.

If intensive therapy with antacid is necessary in a specific case, large doses at frequent intervals are required. For such treatment calcium carbonate with sufficient magnesium carbonate to prevent constipation is probably the drug of choice.

Antacid lozenges which are designed to dissolve slowly when held in the cheek are worthy of serious trial. They present a substantial advantage by producing adequate neutralization with the minimum of antacid drug.

REFERENCES

1. Kirsner, J. B., Palmer, W. L., Levin, E. and Klotz, A. P.: Gastric antacids and antisecretory drugs. Ann. Int. Med. 35:785, 1951.
2. Alvarez, W. C.: The mechanics of the digestive tract. P. B. Hoeber. New York, 1928.
3. Freezer, C. R. E., Gibson, C. S. and Matthews, E.: A contribution to the study of "alkalis" as therapeutic agents. Guy's Hosp. Rep. 8:191, 1928.
4. Johnson, E. H. and Duncan, J.: The chemical testing of antacids. Quart. J. Pharmacy and Pharmacol. 18:251, 1945.
5. Hammarlund, E. R. and Rising, L. W.: A further study of the comparative buffering capacities of various commercially available gastric antacids. J. Am. Pharm. Assoc. 41:295, 1952. Also *ibid.* 38:586, 1949.
6. Lemaistre, J. W., Holbert, J. M. and Grote, I. W.: A study of antacid buffers. J. Am. Pharm. Assoc. 38:595, 1949. Also Holbert et al.: *Ibid.* 37:292, 1949 and 36:149, 1947.
7. Armstrong, J. and Martin, M.: An *in vitro* evaluation of commonly used antacids. Quart. J. Pharmacy and Pharmacol. 5:672, 1953.
8. Lockwood, B. C. and Chamberlin, H. G.: The effect of alkalis on gastric secretion and motility as measured by gastric analysis. Arch. Int. Med. 32:74, 1923.
9. Babkin, B. P.: Secretory mechanism of the digestive glands. P. B. Hoeber, New York, 1950.
10. Davies, R. E. and Longmuir, N. M.: Production of ulcers in isolated frog gastric mucosa. Biochem. J. 42:621, 1948.
11. Cummins, G. M., Grossman, M. I. and Ivy, A. C.: The acid factor in the production of gastro-intestinal ulcers in dogs. Fed. Proc. 6:93, 1947.
12. Kirsner, J. C. and Palmer, W. L.: The effect of various antacids on the hydrogen-ion concentrations of the gastric contents. Am. J. Dig. Dis. 7:85, 1940.
14. Rowlands, E. N., Wolf, H. H. and Atkinson, M.: Clinical assessment of drugs which inhibit gastric secretion. Lancet 2:1154, 1953.
15. James, A. H. and Pickering, G. W.: The role of gastric acidity in the pathogenesis of peptic ulcer. Clin. Sci. 8:181, 1949.
16. Winkelstein, A.: A new therapy of peptic ulcer continuous alkalinized milk drip into the stomach. Am. J. Med. Sci. 185:695, 1932.
17. Cornell, A., Hollander, F. and Winkelstein, A.: The efficacy of the drip method in the reduction of gastric acidity. Am. J. Digest. Dis. 9:332, 1942.
18. Douthwaite, A. H. and Batty Shaw, A.: The control of gastric acidity. B.M.J. 1952, 180.
19. Batterman, R. C. and Ehrenfeld, I.: The ambulant treatment of the peptic ulcer syndrome: the comparative effectiveness and constipating action of antacids. Gastroenterology. 9:141, 1947.
20. Rossett, N. E., Knox, F. H. and Stephenson, S. L.: Peptic ulcer: medical cure by efficient gastric acid neutralization. Ann. Int. Med. 36:98, 1952.
21. Havens, W. P.: Intestinal obstruction caused by colloidal aluminum hydroxide. J.A.M.A. 113:1564, 1939.

THE ETIOLOGY OF ENDOMETRIOSIS

D. B. MONTGOMERY, 5T4

DEFINITION

Novak defines endometriosis as the condition in which tissue resembling more or less completely the uterine mucous membrane occurs aberrantly in various locations.

INCIDENCE

1. *Age*

Endometriosis has been reported in patients ranging in age from 16 to 78 years. However the incidence is highest in the late child-bearing years, with the average between 35 and 40 years.

2. *General Incidence*

Reports on the incidence of endometriosis in laparotomies vary from 5% as reported by Meigs to 29.5% as reported by Sampson with the average figure around 10% reported by most authors. There is little information on the incidence in the general female population.

Meigs found endometriosis was five times as common in private patients as in ward patients, and related this to late marriage, too infrequent and too late child-bearing in private patients.

Cavanagh reported similar findings, but when he considered the virtual absence of pelvic inflammatory disease and lower incidence of fibroids in private cases, the incidence became equal in both private and ward cases.

3. *Marriage, Fertility and Pregnancy*

Cavanagh found that there was a significant correlation between endometriosis and the unmarried state after age 25 years. (He also reported that in private and ward women, who subsequently developed endometriosis, there was no difference in fertility rates regardless of age of marriage.) However, if compared with rates of the average population, infertility was twice as common in women marrying before the age of 30 years, and nine times as common after age 30 years.

As yet it cannot be stated whether endometriosis is a cause or an effect of infertility. Pregnancies have been reported subsequent to conservative surgery for endometriosis.

ETIOLOGY

The etiology of endometriosis is unknown. However there are several factors which may predispose to its development.

(A) Mechanical

(1) *Surgery, Curettage and Insufflation*

Several observers have shown that pieces of endometrium transplanted accidentally or intentionally into an incision readily grew and functioned at the new site. In patients upon whom laporotomies were performed following curettage, blood has been observed dripping from the tubes and collecting in the cul-de-sac. Endometriosis has been produced following insufflation in guinea pigs and rabbits.

(2) *Pathological Anatomy of the Genital Canal*

(a) RETROVERTED UTERUS

Watkins, Hayden and others have performed laporotomies on women with retroverted uteri at the time of menstruation and have observed blood dripping from the tubes and collecting in the cul-de-sac. The incidence of retroverted uteri in endometriosis has been reported with a range of 7 to 52%; however, some believe that retroversion is the effect of endometriotic adhesions, not the cause.

(b) CERVICAL OBSTRUCTION

In cases of cervical strictures following endocervicitis, cervical instrumentation, of cervical tumours, and of congenital atresia of the cervix or vagina, a remarkable degree of dilatation of the vagina, cervix, uterus and tubes may result before retrograde menstruation occurs.

(B) INFLAMMATORY FACTORS

Inflammatory changes are usually seen in and around active endometrial lesions. These changes are probably the local response to a semi-invasive tissue in a foreign location, aggravated periodically by the menstrual cycle—i.e., an effect rather than a cause in the development of endometriosis.

(C) HORMONAL FACTORS

(1) *Response of Ectopic Endometrium to Ovarian Hormones*

Several authors have shown that active endometriotic lesions can respond to ovarian hormones in a manner similar to the response of uterine endometrium. Stilboestrol has been shown to reactivate rectovaginal endometriosis in a postmenopausal woman. Endometrial transplants will develop in normal rabbits, but not in those previously castrated. However one must remember that the ability to stimulate already existing tissue to physiological activity is not the same or necessarily related to the ability to initiate the development of new tissue.

(2) *Relative Tissue Sensitivity to Hormonal Stimulation*

Not all lesions of endometriosis show cyclic activity, and many respond only to estrogen and not to progesterone. Several explanations have been proffered.

(a) Some endometrial lesions may be derived from the functionalis while others are from the basalis.

(b) If ectopic endometrium evolves by metaplasia from peritoneal and subserosal cells, then at any one time there must be several stages of maturity represented in different lesions, of which the more mature would respond more readily to hormonal stimulation.

(3) *Age Incidence*

Endometriosis occurs in the majority of cases during the latter part of the child-bearing period, usually ceasing at the menopause.

(4) *Infertility*

The relative sterility is estimated at 50-90%. Infertility is often noted early in sexual life, preceding rather than following the known development of endometriosis inferring that it may be caused by the same factors which initiate the development of endometriosis.

(5) *Coincident Pelvic Pathology*

Many authors have reported an increased incidence in patients with endometriosis who have been operated upon of fibromyomata of the uterus, uterine endometrial hyperplasia, endometrial polyps, and follicular cysts. This would

infer that endometriosis is but one of the manifestations of hyperestrinism in women. However endometriosis is rarely diagnosed prior to operation which is usually done for other reasons with endometriosis as an incidental finding. Hence one cannot draw conclusions for there may be many women with asymptomatic endometriosis.

(6) *Cyclic Stimulation Theory*

Meigs, finding a higher incidence of endometriosis in private than in ward cases, believes that it is the physiologic result of an abnormally uninterrupted menstrual career.

All of the above factors, mechanical, inflammatory, hormonal, only infer rather than prove conclusively any etiology.

PATHOGENESIS

When few facts are known concerning the pathogenesis of a condition, one meets a variety of theories indicating that no single explanation has been found acceptable.

(A) Transplantation of Endometrial Tissue from the Uterus

(1) *Implantation Theory*

This theory proposes that endometrial tissue is implanted in ectopic sites following retrograde menstruation through the tubes. Sampson in 1922 postulated this theory on the evidence that:

(a) The presence of endometriosis can be demonstrated in cases of retroversion with obstruction to the uterine or cervical canal.

(b) Endometriotic lesions are distributed, often bilaterally, in the dependent portions of the pelvis.

(c) The tubes are usually patent and endometriosis is rare in cases of pelvic inflammatory disease.

(d) Endometrium can be experimentally implanted on the peritoneum.

Other authors have verified these findings. Against this theory, Novak and Ewing point out that endometrial islands are usually found deeper with the tissues than would be expected of surface implantations. Novak also doubts the presence of viable endometrial tissue in the menstrual reflux. Although endometrial tissue has been identified in the menstrual reflux, and this has been grown for short periods, this does not prove that the tissue has sufficient viability to sustain it until implantation can occur. Indeed, Mackee transplanted endometrial tissue to the anterior chamber of the eye in 61 monkeys, and in 432 estrus cycles he did not observe a single instance of re-implantation of shed fragments, although the original implants were easily established.

Thus Sampson's implantation theory may explain certain cases of Endometriosis existing with uterine retroversion which have been previously subjected to curettage or tubal insufflation during episodes of bleeding.

(2) *Mechanical Transplantation Theory*

Endometrial tissue can be transplanted surgically either accidentally or intentionally as shown by Sampson and others, explaining the presence of lesions in laporotomy scars following operations in which the uterotubal cavity was opened.

(3) *Metastases Theory* (Lymphatic and Haematogenous)

Halban first proposed this theory in 1924, and it still best explains the very rare examples of endometriosis of the extremities. Halban found glandular and

stromal cells in lymph nodes draining the uterus, but evidence is not complete as to whether these are due to metastases of endometrial cells or due to metaplasia of lymphatic endothelial and stromal cells.

(B) Ectopic Endometrium Developed In Situ from Local Cells

(1) *Coelomic Metaplasia*

This theory has gradually evolved from observation and experiments made by many men, particularly Waldeyer, Iwanoff, Meyer, Novak, Heim and Gruenwald. It proposes that the Mullerian duct is derived from the embryonic coelomic epithelium and mesenchyme and forms most of the female genital tract including the endometrium and hence other adult derivatives of these embryonic coelomic cells may retain the potentiality of forming tissue which is histologically and functionally indistinguishable from endometrial tissues.

Gruenwald has demonstrated the embryological basis of this theory with human and chick embryos. This theory would explain endometriosis reported in the umbilicus, extremities, vagina and pleura, which the tubal reflux theory fails to explain. The coelomic metaplasia theory permits a physiological explanation based on embryological as well as pathological observations for spontaneously occurring endometriosis in any portion of the body in which it has been reported.

(2) *Ovarian Metaplasia Theory*

King in 1933 proposed that endometrium-like haemorrhagic cysts of the ovary resulted from changes in cystic atretic follicles and cystic corpora lutea. This was based on similar histology, and is supported by the following findings:

(i) High incidence of infertility with endometriosis suggests primary ovarian dysfunction.

(ii) Endometriosis occurs most frequently in the ovaries. These reports may be widely interpreted, and proof or disproof of the theory is as yet impossible.

(3) *De-differentiation Theory*

Brines and Bain in 1943 postulated that myometrial cells may undergo a process of de-differentiation into less mature cells which possess the potentiality of (i) forming the interstitial cells of the endometrial stroma, and (ii), differentiating into epithelial cells to form glands within that stroma. This theory is feasible but extremely difficult to prove.

(4) *Embryonic Cell Rest Theory*

This theory postulates the possibility that embryonic cell rests of paramesonephric or mesonephric tissue might grow during adult life. No actual proof or disproof of the growth of paramesonephric tissue is available at present. The theory concerning the possible growth of mesonephric tissue, suggested by von Recklinghausen in 1895, has been discarded because of known differences in the embryonic development of mesonephric and paramesonephric ducts.

(5) *Direct Extension Theory*

Cullen showed that in 55 of 56 adenomyomatous uteri the gland elements of the ectopic tissue were a direct continuation of uterine endometrium. The extending endometrial tissue takes the line of least resistance, whether it be between muscle bundles (Cullen) or through lymph channels (Sampson, Henderson). This theory is considered to be the most frequent mode of development of internal endometriosis, both glandular and stromal.

(C) Combined Theories

(1) *Uterotubal Theory*

This postulates that bits of healthy tissue break off either from the mucosal surface of the adenomyotic areas to migrate out the tubes, or from the serosal surface of adenomyotic areas to travel elsewhere in the pelvis, to implant and produce external endometriosis. Novak has observed adenomyosis with endometriosis in 42 out of 243 cases. This theory is interesting but requires more evidence.

SUMMARY

Endometriosis occurs most often during the age period 35-40 years and is found in 10% of pelvic laporotomies. The etiology is obscure. Clinical and pathological evidence suggests hormonal factors are concerned. Concerning the etiology and pathogenesis, many theories have been given to explain the observations and many inferences made, but as yet there is no single concrete proven cause and mechanism. Two theories emerge as the most plausible, the implantation theory and the coelomic metaplasia theory, but neither is all-embracing.

REFERENCES

1. Novak and Novak: Textbook of Gynecology, Williams and Wilkins, 1952.
2. Cavanagh: Am. J. Obst. and Gyn., 61: 539, 1951.
3. Leffler et al.: Am. J. Obst. and Gyn., 62: 1148, 1951.
4. Haydon: Am. J. Obst. and Gyn., 43: 704. 1942.
5. Frank and Geist: Am. J. Obst. and Gyn., 44: 652, 1942.
6. Gruenwald: Am. J. Obst. and Gyn., 44: 470, 1942.
7. Henderson: Am. J. Obst. and Gyn., 41: 694, 1941.
8. Novak: Am. J. Obst. and Gyn., 56: 634, 1948.
9. Sampson: Am. J. Obst. and Gyn., 40: 549, 1940.
10. Sampson: Am. J. Obst. and Gyn., 50: 597, 1945.
11. Sampson: Arch. Surg., 3: 245. 1921.
12. Meigs: New Eng. J. Med., 226: 147, 1942.
13. Novak: Am. J. Obst. and Gyn., 12: 484. 1926.
14. Witherspoon: Surg., Gyn. and Obst., 61: 743, 1935.
15. Fallas: West. J. Surg., Obst. and Gyn., 59: 448, 1951.
16. Fallon: New Eng. J. Med., 235: 669, 1946.
17. Internat. Abstr. Surg., 86: 313, 19 .

FEATURE

REPORT OF CONFERENCE ON MEDICAL EDUCATION

J. A. MacFARLANE, M.D.

The first International Conference on Medical Education was held in London, England, from August 24th to August 29th. The organization was undertaken by the Executive Committee of the W.M.A. The immediate arrangements were made by a committee in England under the chairmanship of Sir Lionel Whitby, the Vice-Chancellor of Cambridge University.

Representatives from 59 countries, including Jugoslavia, attended the conference. Neither Russia nor any of the other Communist countries attended. Six Canadian schools sent representatives and three of them contributed papers. Arrangements were made for immediate translation, and the members of the conference could listen to any speaker in one of three languages, English, French or Spanish.

After the initial general session the conference divided into four groups, coming together again for the last session when rapporteurs from each of the groups gave a summary of his impressions of the highlights in each seminar. The subjects of the four sections were as follows:

(1) the requirements for entry into medical schools
(2) aims and content of the curriculum
(3) techniques and methods of medical education
(4) preventive and social medicine.

The full report of the proceedings will be available in a volume published by the Oxford University Press in the early spring of 1954. Initial reports were published in the B.M.J. of August 29th, 1953, and every student should at least read the speeches in the opening session of Sir Lionel Whitby and Sir Richard Livingstone, which are reported in full in that issue.

This was something more than just another conference. It did not seek to make recommendations. It was a forum where educators from many lands discussed their ideas and problems in teaching the youth of the modern world the principles of medicine as we understand it in 1953. Perhaps in no other field of human endeavour is it possible to achieve such a degree of mutual understanding on an international level as in the field of medicine. Here indeed once the barriers of language have been overcome, do men from all countries speak with common understanding. Illness, its prevention and its management, may vary somewhat with environmental and climatic conditions, but essentially, human anatomy, human physiology, and the pathology of human disease varies but little. In a world where there is so much difficulty in reaching common ground in matters of law, of politics, and of diplomacy it is all the more gratifying to note in a conference such as this, a common idealism in medicine, and a common interest in improving the methods by which present day medical knowledge may be communicated to a new generation of physicians.

THE SURGICAL MANAGEMENT OF PERIPHERAL ARTERIAL ANEURYSMS

W. G. FRANCIS, 5T4

DEFINITION:

A peripheral arterial aneurysm may be defined as a localized or segmental dilatation in the course of a major peripheral artery, occurring either spontaneously or secondary to an injury to the vessel wall.

ANATOMY:

These aneurysms can occur anywhere in the course of any peripheral artery, but occur most commonly in the carotid, subclavian, axillary, brachial, radial, ulnar, femoral, popliteal, and anterior & posterior tibial arteries.

CLASSIFICATION:

1. TRUE ANEURYSMS: those whose walls are composed of the component parts of the arterial wall. The aneurysmal sac is usually fusiform in shape, but may obtain saccular form with pressure from surrounding structures. The wall of the artery is weakened by intrinsic disease, segmental in character; this weakened arterial wall begins to dilate, eventually resulting in a symmetrical fusiform swelling, the "aneurysmal sac".
2. FALSE ANEURYSMS: those whose walls are composed of fibrous tissue and laminated blood clots; never do they contain any of the component parts of the arterial wall.

Aneurysms may also be classified as:

1. FUSIFORM: in which the entire circumference of the vessel is weakened, with a resulting symmetrical dilatation.
2. SACCULATED: in which the aneurysm projects from the artery as a globular mass, because of a weakness at one point in the media; or occasionally due to the restricting pressure of surrounding structures, such as fibrous tissue planes, muscles, or bones.

AETIOLOGY:

The incidence of arterial aneurysms has increased markedly in the last twenty years, and the cause of this is directly related to the aetiology:

1. TRAUMATIC (20% of peripheral arterial aneurysms):

   Most of these used to be due to gunshot or stab wounds; but nowadays, with the increased rate and distance of travel, modern mechanical methods of transportation, and modern machinery, a great many puncture wounds are occurring in highway and industrial accidents. Also surgery and chemotherapy have improved the survival rate, so that more people are living longer to develop aneurysms. In the popliteal arteries and in a subclavian artery just distal to a cervical rib, it is thought that certain aneurysms which develop are due to the repeated minor trauma occurring in these areas.

2. DEGENERATING DISEASES (80% of peripheral arterial aneurysms):

(a) *Syphilis*—aneurysms are now quite rare, due to better control and treatment of syphilis..

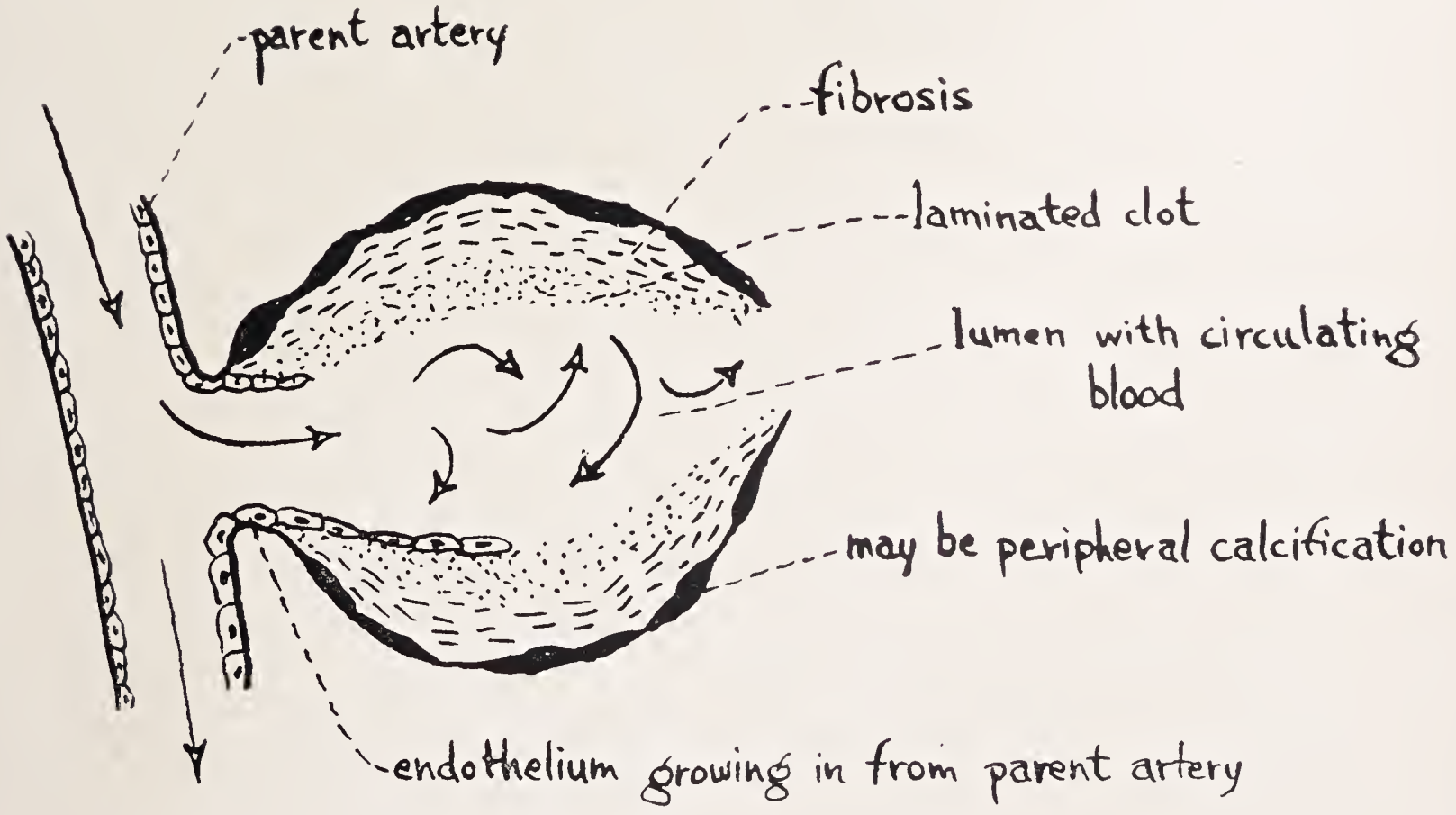
(b) *Bacterial Endocarditides*—the resulting "Mycotic Aneurysms" due to pyogenic bacterial infection of a segment of arterial wall are also rare.

(c) *Arteriosclerosis*—there is now a much longer life expectancy; 40% of men and 18% of women over 40 show some degree of arterial calcification, and these are all candidates for aneurysms.

PATHOLOGY:

In the case of *Traumatic Aneurysms*, due to puncture wounds, fractures, or anything penetrating the artery, a haematoma will form outside the ruptured arterial wall. This haematoma is limited by the surrounding tissues; it may pulsate, or may compress other vessels and cause gangrene which necessitates immediate surgery. The periphery of the haematoma rapidly develops a fibrous coat, leaving a hollow centre with the squirting blood from the artery, bordered by a laminated clot layer. The lumen of the mass may enlarge due to the pressure of the circulating blood within it. Thus from within outwards, the mass consists of hollow lumen containing blood from the parent artery, an endothelial layer which grows in from the parent artery within a weak, jelly-like laminated clot, gradually becoming more fibrous, until even calcification may develop in the outer layers of the wall with time. The whole mass pulsates in time with the heart beat. The aneurysm may enlarge or rupture with slight trauma. If the vessel wall is merely weakened, then a spot may give way like an inner tube bulging through a defect in a tire casing.

In the case of the *Aneurysms due to Degenerating Diseases*, the resulting pulsating mass may be fusiform in shape (with weakening of the arterial wall over a considerable time) or saccular (with



an acute rupture contained by the surrounding tissues).

True aneurysmal sacs commonly rupture, resulting in pseudopod-like false aneurysms which communicate with the lumen of the true aneurysm.

Aneurysms may enlarge and displace other organs; they often become adherent to bowel or ureter, etc., with resulting pathological changes in these organs, and the consequent symptomatology which may bring the patient in to see the doctor. The pulsating force of the aneurysm may erode bone, resulting in neurological symptoms.

The typical *syphilitic aneurysm* is a saccular defect in the thoracic aorta, following syphilitic aortitis.

DIAGNOSIS:

40% of peripheral arterial aneurysms are found accidentally on examination; 60% are found in patients who present with symptoms due to the aneurysm.

1. Hemorrhage—in traumatic aneurysms.
2. An expansile, pulsatile, localized swelling or mass in the course of a major peripheral artery; a systolic thrill may be felt, and a systolic murmur synchronous with the heart beat may be heard (with varying degrees of pitch and intensity), due to the whirling blood in the sac; the sac tends to enlarge gradually, according to its site and surrounding structures, the size of the vessel, the degree of the wall defect, and the stage of degeneration (if due to degenerating disease).
3. Obliteration of the main artery proximal to the swelling causes the disappearance of all clinical manifestations except the swelling, which decreases to some extent (according to the amount of laminated clot in the lumen). This is the *Diagnostic Triad* for an aneurysm—with pressure on the artery proximal to the swelling, there is a decrease in size, cessation of pulsations, and cessation of murmurs.
4. Pain—due to pressure of the mass against some sensitive structure such as a nerve; or due to ischaemia distally, with claudication.
5. Such confusing complications as venous thrombosis, secondary to enlargement of the sac; a pulmonary embolus may even occur with pressure of the sac on a vein.
6. X-Ray Delineation with soft-tissue technique may reveal a calcium shadow outlining the aneurysm, especially in those due to arteriosclerosis.

   Arteriography will also outline the defect nicely.

TREATMENT:

In approximately 4% of these aneurysms, spontaneous resolution may occur; the sac becomes obliterated by clot, which forms a firm coagulum. In these cases, the only treatment considered is sympathectomy. This spontaneous resolution has prompted the "watch and wait" attitude to some extent; but this attitude usually results in eventual rupture of the aneurysm and loss of the distal part of the extremity.

Thus Surgical Therapy is the only proper treatment, and its success depends upon the cause of the aneurysm, the length of time it has been present, and the site of the vessel involved.

Surgical treatment consists of careful anatomical dissection, and all forms of vascular suturing and grafting; this necessitates great care, and can be very

tedious. Surgical sympathectomy is of value as an adjunct in the treatment of most aneurysms.

There are two principles involved in the treatment: complete obliteration of the aneurysm, and the preservation of an adequate and sustaining normal metabolism, with adequate blood flow distal to the aneurysm through either the main arterial channel or its collaterals. Therefore the problem is to arrest all blood flow into and through the aneurysm, while at the same time maintaining an adequate blood supply below the anatomical site of the aneurysm. Control of the blood supply proximal to the aneurysm before operation is essential, at both the proximal and distal poles of the aneurysmal sac. This is accomplished by the application of a tourniquet to the extremity if feasible; if a tourniquet cannot be used, the proximal artery must be thoroughly exposed and a proximal ligature applied (rubber dam tubes, elastic bands, or Potts' ductus clamps)—otherwise loss of limb or even life may result.

The figures quoted under the following methods of therapy are those provided by Pratt, from his series described in 1952.

1. *Excision of the aneurysm with end-to-end anastamosis of the artery:*
   purpose—to restore the original continuity of the artery.
   application (10%)—wherever possible, since no collateral system of vessels can carry the same arterial load as the original vessel.
   method—proximal and distal control of the blood flow, excision of the sac; the vessel is dissected free, and re-routed if necessary, the free ends of the vessel are sutured together with arterial silk; [interrupted sutures are used in large vessels with much tension in their lumens (such as the aorta), or in the vessels of children (to allow for growth of the vessels)].
2. *Excision of the aneurysm with repair of the artery (reparative or aneurysmorraphy):*
   purpose—to repair the artery.
   application (8%)—traumatic aneurysms.
   method—proximal and distal control of the blood flow, sac opened and evacuated, repair of the opening in the arterial wall.
3. *Excision of the aneurysm with autogenous vein or homologous artery graft:*
   purpose—to replace the artery.
   application (12%)—young patients (unsuccessful in elderly people).
   method—autogenous vein grafts are usually used, since the excision of arteries will obviously damage the donor site; however, grafts of arteries from cadavers have been effective, these arteries having been preserved in deep freeze for up to forty-five days. "Artery Banks", however, are so far very new and uncommon; but they may well become very popular in the near future.
4. *Obliteration of the aneurysmal sac with preservation of the collaterals (Matas' endo-aneurysmorraphy)*—a fifty-year old method, recently supplemented by the use of muscle implants to obliterate the sac (Pratt):
   purpose—to remove the aneurysm without loss of the distal blood supply.
   application (37%)—aneurysms of more than three or four months duration, in which collateral circulations have had time to develop.

The method of choice if there is any question about other methods of therapy.

method—determine the state of the collateral circulation preoperatively (or develop the collateral circulation by sympathectomies as necessary) proximal and distal control of the blood flow, sac opened and contents removed; suture all collateral openings within the sac (thus obliterating the sac without its removal, preventing destruction of the collateral vessels).

Pratt has added the insertion of a muscle core into the sac, thus making it easier to suture the sac closed.

5. *Proximal obliteration of the artery entering the aneurysm:*

purpose—to fill the aneurysm with clotted blood by stopping the flow through the sac. This has been unsuccessful as a rule, due to retrograde flow into the aneurysm, with resulting persistence of the aneurysm and frequently rupture.

application (7%).

method—the proximal obliteration may be complete or partial (with soft rubber, polythene, or tantalum).

Anel's Operation: the main artery is ligated as near the proximal pole of the sac as is anatomically feasible. This method is currently popular in the case of mycotic aneurysms, where there is danger of spreading the infection; it can be life-saving for ruptured aneurysms; and it is popular for carotid, subclavian, or innominate artery aneurysms.

Reid's Technique: a fascial plug is placed within the artery proximal to the ligation point.

6. *Peri-aneurysmal irritation:*

purpose—gradual obliteration of the aneurysmal sac, while allowing collaterals to develop during the time of closure.

application (8%)—aneurysms not otherwise amenable to treatment.

principle — polythene is wrapped around the sac, with a cover of cellophane to protect the surrounding structures. The diacetyl phosphate in the polythene causes an irritant reaction in the vessel wall, resulting in gradual thickening and closure of the wall.

7. *Intra-saccular wiring:*

purpose—the wire fills the space within the sac, then clotting takes place around the wire, and eventually the sac is obliterated by fibrosis. Blakemore introduced a coagulation current through the intra-saccular wire, a method which has not received wide approval.

application (7%)—in abdominal or thoracic aneurysms of the aorta.

method—Pratt uses steel alloy wire without coagulation current, inserting as much wire as possible by a stilet introducer; he has inserted up to 400 feet of wire into some aneurysms.

8. *Combined intra-saccular wiring and polythene wrapping:*

purpose—gradual obliteration of the sac with the development of collaterals.

application (2%).

9. *End-to-end arterio-venous shunt distal to the aneurysm* (anastamosis of the peripheral end of the artery to the proximal end of the vein):

purpose—to remove peripheral resistance and increase the rate of flow distal to the aneurysm, thus de-

creasing the wall pressure within the sac (by hydrodynamic principles).

application (7%)—in abdominal or thoracic aneurysms of the aorta.

method (Babcock, 1925)—the carotid artery above the aneurysm is united end-to-end with the proximal end of the jugular vein.

10. *Wrapping with steel mesh cloth (Babcock):*

purpose—to reinforce the aneurysmal sac.

application (2%)—advanced arteriosclerotic aneurysms of the abdominal aorta, in conjunction with intra-saccular wiring.

method—an innocuous, non-irritative fine steel mesh wire is wrapped around the sac; this eventually disappears into the wall of the sac.

Pratt uses intra-saccular wiring in conjunction with the steel mesh wrapping of the aneurysm, to give intra-saccular clotting and fibrosis in addition to the reinforcement of the sac.

Summary of treated arterial aneurysms—St. Vincent's Hospital, New York, 1952 (not including sympathectomy):

Aetiology	*Site*	*Main symptoms*	*Prognosis*	*Treatment*
1. Trauma (20%)	Any vessel	Mass Systolic bruit Pain Ischaemia	Good with operation	1. Excision and anastamosis of artery. 2. Repair of artery. 3. Autogenous vein or homologous artery graft. 4. Obliteration of the aneurysm.
2. Degenerating diseases (80%)—arteriosclerosis, syphilis, bacterial endocarditides	Any vessel; mainly aorta	Mass Systolic bruit Pain Ischaemia Calcification seen on X-ray	Poor; therapy eases the symptoms and prolongs life.	Same as above—but usually 4. Obliteration of the aneurysm.

SUMMARY:

1. Aneurysms are increasing in incidence, due to modern mechanized living and to the increased life expectancy. 20% of aneurysms are due to trauma; 80% are due to degenerating diseases.
2. There are two types of aneurysms—true and false—each with its subgroups.
3. Early diagnosis of aneurysms is essential, e.g. to prevent gangrene. The Diagnosis is simple, and is made by the symptoms and signs:
   —an expansile, pulsatile, localized swelling in the course of a major peripheral artery, pulsating synchronously with the heart; along with a systolic murmur of varying intensity or pitch.
   —obliteration of the main artery proximal to the aneurysmal swelling causes the disappearance of all clinical manifestations except the swelling, which decreases to some extent.
4. Prognosis:
   (a) traumatic aneurysms—prognosis is good with operation.
   (b) aneurysms due to degenerating

diseases—prognosis for cure is poor, but life can be prolonged and symptoms (especially pain) can be alleviated.

5. Treatment depends on the cause, the site, and the extent of the pathology; and necessitates skill and experience in judgment, since no two cases are the same.
6. The treatment of choice is as follows:
   (1) adequate proximal and distal control of the blood flow through the sac (tourniquet, rubber dam, ligatures, Potts' ductus clamp).
   (2) adequate collateral circulation must be present, or must be developed and sustained pre-operatively—usually by sympathectomy (Gage's physiological method).
   (3) surgical sympathectomy is of value as an adjunct to therapy for nearly all aneurysms.
   (4) post-operative prolongation of clotting time is advisable, to prevent plugging of the vessel.

principles—

(1) complete obliteration of the aneurysm.

(2) preservation of an adequate sustaining blood flow distal to the site of the aneurysm, through either the main artery or its collaterals.

(a) for Traumatic Aneurysms: any measure restoring the continuity of the vessel—
   1. excision with end-to-end anastamosis.
   2. excision with repair of the artery.
   3. excision with autogenous vein or homologous artery graft.

(b) for Aneurysms due to Degenerating Diseases:
   —the obliterative procedure of Matas (endo-aneurysmorraphy) with Pratt's method of muscle implantation.

(c) for "Hopeless Aortic Aneurysms": palliative procedures, to prolong life and alleviate symptoms (especially pain)—
   1. peri-aneurysmal irritation with intra-saccular wiring.
   2. wrapping with steel-mesh cloth with intra-saccular wiring.

REFERENCES

Surgical Clinics of North America, Aug. 1953—"The Treatment of Peripheral Arterial Aneurysms"—Gage.

"Surgical Management of Vascular Diseases"—G. H. Pratt.

Angiology, Dec. 1952—"The Surgical Treatment of Arterial Aneurysms"—G. H. Pratt.

"Vascular Disorders of Limbs"—Sir Thomas Lewis.

"Surgery of the Vascular System"—Bertram M. Bernheim.

CASE REPORT

JOSEPH WAGNER, 5T4

Chief Complaint

October 20, 1953

Mr. P. B., a 53 year old Indian, was admitted to hospital with the following chief complaints—blurred vision for 6 months, headache for 5 months, repeated vomiting for 2 weeks, and increasing drowsiness and weakness for 1 week.

History of Present Illness

In the spring of 1953 this patient had consulted his family physician in northern Ontario because of failing vision. His doctor did not examine him but advised him to see an ophthalmologist, which the patient failed to do.

In July, while working on a lumber pile, the patient fell and as a result a number of ribs were fractured. He did not lose consciousness. However, following this accident, he began to complain of headaches and these have persisted until this time.

In October, the patient was admitted to a rural hospital for the extraction of a number of carious teeth under general anaesthesia. Following this procedure he began to vomit repeatedly. The patient's fluid and electrolyte balance was corrected by intravenous therapy and later a gastric series was done, but this failed to reveal any abnormality which might account for the vomiting. At this time the patient was weak but able to walk, complained of headache, vomited intermittently, and did not appear confused although his memory seemed poor. He was then referred to a hospital in Toronto. The remainder of the history was unobtainable due to the patient's condition.

Physical Examination

The patient was a middle-aged Indian in a very drowsy, semi-conscious state. There were no cranial deformities and no intracranial bruit could be heard. ENT examination was negative. The neck was supple, there was no lymphadenopathy or enlargement of the thyroid, and the trachea was midline. The chest was symmetrical, expanded well, and was clear to percussion and auscultation. The heart rate was 68 and regular. The apex beat was palpable in the fifth left intercostal space within the midclavicular line. There were no murmurs. The BP was 170/90. The abdomen was soft, non-tender, and the liver, spleen and kidneys were not enlarged.

On neurological examination, the patient was very drowsy and responded sluggishly to questions. He was disorientated as to time and place. His attention wandered, and was so variable that sensory examination was impossible. Visual acuity was markedly impaired. Examination of the fundi revealed severe bilateral papilloedema with haemorrhages. The right pupil was very slightly larger than the left but both reacted briskly to light. There was no nystagmus. The right corneal reflex was absent. There was a complete upper and lower right facial weakness. The tongue deviated to the right on protrusion. There was a slight ten-

dency for the right arm to drift when held extended. The patient was generally weak and could not stand. Co-ordination was good. The sensory system could not be properly examined. The deep tendon reflexes were sluggish but were equal bilaterally. The abdominal reflexes were absent. Both plantar responses were downgoing.

Discussion

The history of headaches, vomiting, increasing drowsiness, and the finding of bilateral papilloedema indicated that this patient had increased intracranial pressure. This was felt to be due to a space-occupying lesion which could not be accurately localized with the information thus far available. The history of injury suggested the possibility of subdural haematoma, while the history of tooth extraction required that brain abscess be considered as a possible diagnosis.

Progress and Course in Hospital

October 21, 1953:

Routine X-rays of the skull showed a questionable erosion of the right porus acusticus, and a calcified pineal gland which was very slightly (about 3 mm.) displaced to the left.

An electro-encephalogram showed an abnormal record in which the disturbance could not be localized but it was considered to be compatible with a diagnosis of subdural haematoma.

October 22, 1953:

Bilateral exploratory burr holes were made in the upper mid-temporal and high postero-parietal regions of the skull. The brain appeared quite tense but there was no evidence of extradural or subdural clot. The wounds were closed.

October 23, 1953:

A ventriculogram was done. This showed the lateral and third ventricles to be grossly enlarged. The aqueduct was elevated and displaced to the left. The fourth ventricle was also displaced to the left, narrowed from side to side, and concave to the right. These findings indicated a space-occupying lesion in the posterior fossa lying far forward alongside the aqueduct on the right side.

The lesion having been located in the right cerebello-pontine angle, a provisional diagnosis of acoustic neuroma was made.

A craniotomy was performed exposing the posterior fossa and a tumour was identified in the right cerebello-pontine angle. The tumour was resected. Subsequently, microscopic examination showed the tumour to be a classical neurofibroma composed of long slender cells with spindle-shaped nuclei which in some places were arranged in palisades while in other places there was a suggestion of whorling. There were no mitotic figures.

The patient's post-operative course was satisfactory. Within two weeks he was able to walk around the ward. He was well orientated but still somewhat apathetic. The only neurological deficit remaining aside from an eighth nerve deafness was a right facial palsy.

November 12, 1953:

Accordingly, a hypoglossal-facial anastomosis was carried out under general anaesthesia to correct the facial palsy. Again the patient made a good recovery, and on November 26th was discharged from hospital.

Comment:

The acoustic neuroma is a benign encapsulated tumour arising from the

eighth cranial nerve. It grows slowly until it reaches the size of a golf ball and manifests itself by pressure effects on surrounding structures and by causing increased intracranial pressure.

Surgery offers real hope for the patient with an acoustic neuroma but the technical difficulties are great and the removal of these tumours represents one of the most formidable operations in surgery. It is important, as it is in all brain tumours, to arrive at an early diagnosis before the optic discs are irreparably damaged by prolonged choking.

ACKNOWLEDGMENT

It is a pleasure to acknowledge the co-operation of the Neurosurgical Service of the Toronto General Hospital in the preparation of this report.

RECENT ACCESSIONS TO THE MEDICAL READING ROOM

Anderson, W. A. D.: **Synopsis of pathology.** 3rd ed. 1952.
Bull, H. C.: **X-Ray interpretations.** 2nd ed. 1951.
Davidson, L. S. P.: **The principles and practice of medicine.** 1953.
Duncan, C. G.: **Diseases of metabolism.** 3rd ed. 1953.
Frazer, J. E.: **A manual of embryology.** 3rd ed. 1953.
Garrod, A. E.: **Diseases of children.** 5th ed. 1953.
Grant, J. C. B.: **A method of anatomy.** 5th ed. 1952.
Hamilton, W. J.: **Human embryology.** 2nd ed. 1952.
Holmes, G.: **Clinical neurology.** 2nd ed. 1952.
Joslin, E. P.: **Treatment of diabetes mellitus.** 9th ed. 1952.
Jukes, T. H.: **B Vitamins for blood formation.** 1952.
Kreig, W. J. S.: **Functional neuroanatomy.** 2nd ed. 1953.
Kuntz, A.: **The autonomic nervous system.** 4th ed. 1953.
Maximow, A. A.: **A textbook of histology.** 6th ed. 1952.
Marsh, D. F.: **Outlines of fundamental pharmacology.** 1951.
Mollison, P. L.: **Blood transfusions in clinical medicine.** 1951.
Rhodes, A. J.: **Textbook of virology.** 2nd ed. 1953.
Scobee, R. G.: **The oculorotary muscles.** 2nd ed. 1952.
Sharpe, W.: **Brain surgeon.** 1952.
Walter, W. G.: **The living brain.** 1953.
Zabriski. L.: **Nurses handbook of obstetrics.** 9th ed. 1952.

ABSTRACTS

Acute Hemolytic Anemia Associated with Infectious Mononucleosis: Hall and Archer. New England Journal of Medicine. Dec. 10, 1953, pp. 973–975.

The absence of anemia in infectious mononucleosis is generally accepted and this "fact" is often useful as an aid in differential diagnosis of infectious mononucleosis and leukemia. Most writers agree that anemia of appreciable degree does not appear in infectious mononucleosis unless associated with some complicating factor such as hemorrhage or dietary deficiency. In a study of 300 cases. Read and Helwig found only 6 cases with concomitant anemia; of these 3 were associated with a rapidly developing leukopenia and thrombocytopenia; the anemia being part of this pancytopenia.

The occurrence of acute hemolytic anemia in association with infectious mononucleosis has rarely been reported. The authors describe one case and review seven others.

In 1943, a case was reported by Dameshek to have occurred following sulfadiazine therapy during infectious mononucleosis. The authors feel that the most likely causes of acquired hemolytic anemia are: (1) direct action of a virus, (2) development of hemolytic immune bodies, (3) hypersplenism, and these are discussed.

It is interesting to note that a favorable response to Cortisone is described.

F.P.C.

Fatal Hemolytic Transfusion Reaction Caused by Sensitization to a New Blood Factor "U": Weiner, Unger and Gordon.

A case is described and it is illustrated how the causative factor was found not to be associated with A-B-O, M-N, Rh-Hr or K-k systems. The distribution of this factor, as found by many tests, would exclude its relationship to any other blood factor described to date.

In one month the authors have noted three cases of this nature. However, the others were found to be due to Kell factor and hr′ factor respectively.

The authors indicate their strong feelings in the following statement: "It is evident that blood grouping at present is a highly specialized field, so that these delicate tests must be carried out only by specially trained persons, if fatal hemolytic reactions are to be avoided. Certainly the practice of delegating performance of grouping and cross-matching tests to interns with only a very incidental interest in the subject and very little training, is to be condemned. In large hospitals there should be no problem in setting up an adequate blood grouping department, while in smaller hospitals use could be made of a central blood grouping laboratory.

The new blood factor, "U", was found to be present in everyone of 690 Caucasoids tested and in 421 of 425 Negroids tested.

F.P.C.

Hypothermia*: Churchill-Davidson, McMillan, Melrose & Lynn. Lancet: Nov. 14, 1953, pp. 1011.

Since the difficulty of maintaining adequate flow of oxygenated blood to vital organs is such a great obstacle to progress in cardiac and cerebral surgery, interest was focussed on new methods of decreasing the body metabolism. The authors were most interested in achieving this result by decreasing the body temperature, a method which was used in Napoleon's retreat from Russia and has been advocated more recently for cancer and cardiac surgery by Smith & Fay—1940, Bigelow et al.—1950, Juvenalle et al.—1952. Delorme—1952, and Cookson's group in 1952.

After trials of such methods as: cooling blood by artificial A-V anastomosis; cool-

ing pleural and peritoneal cavities with either cold water or a cooling coil, it was found that the simplest, safest and most satisfactory way was surface cooling.

The authors give full detailed description of carefully controlled experiments which they performed at Buckston Brown Research Farm, Royal College of Surgeons.

The results indicate simple and safe reduction of body temperature provided rectal temperature is not less than 26°C. Below this, cardiac arrythmias are the rule and may pass into ventricular fibrillation. It may be that the decreased blood pressure, cardiac output and dissociation of O_2 can account for cardiac anoxia to produce arrythmias. Juvenalle (1952) suggested increased irritability of pacemaker and conduction tissues by cold.

The conclusions reached were:

1. The method of decreasing body temperature is not important, but surface-cooling is simplest.
2. Body temperature must NOT be reduced below 26°C. and an ECG should always be displayed prominently.
3. Hypothermia may offer advance to cardiovascular surgery but at temperatures below 25°C cardiac irritability increases dangerously.
4. The younger the subject, the greater the margin of safety.

The pulmonary complications which occurred following rewarming could not be adequately explained.

F.P.C.

Variability of Course of Guillian-Barre Syndrome: Boshes & Sherman. Neurology, Nov. 1953, pp. 789–799.

Initially (1916) Barre, Guillian and Strohl described a syndrome of paralysis of peripheral musculature which pursued a benign course ending in recovery.

In 1936 Guillian restated his position, saying that his type of polyradicular neuritis could be identified by two important features: (a) a protein content in the spinal fluid of 1-2 Gm. ("cases with slight albuminosis of 0.3-0.4 Gm do not belong to the syndrome or must be regarded as instances of the abortive form") (b) recovery in all cases.

In 1938—Guillian and Barre agreed that the disease could be fatal and that the protein need not be so high. At this time they added to the simple spinal form, three others (mixed mesenchephalic, pure mesenchephalic and spinal types).

Later, Brown and Baker classified the disease into five types: abortive or mononeuritic, polyneuritic, myelitic, bulbar, and cerebral.

Lewy included Landry's paralysis in this syndrome and felt that it only varied in its course and severity. This was supported in the article "Landry-Guillian-Barre Syndrome", by Hoymaker and Kernohan, who also included "acute infectious polyneuritis" in the syndrome. Their concept of the disease was a "polyradiculo-neuropathy which may begin in any peripheral neurons, spinal or cranial, circumscribed or widespread; may affect predominantly the motor or sensory neurons, or both to the same degree; it may remain essentially radicular, or may extend into the CNS at any point, and either ascend or descend, the outcome usually dependent on a degree of involvement of respiratory or cardiac nerves. The changes in the amount of protein and the number of cells in the spinal fluid are regarded as merely incidental to the disorder."

The usual picture is that of an acute or subacute onset of weakness with paresthesias or sensory loss. This may progress for a few days or weeks. A fatal termination is not uncommon. Generally, if patient survives there is a gradual resolution with or without residues. Relapses do occur, though uncommon, and are felt by some to indicate an incorrect diagnosis.

The authors again stress the variability of course and present four cases to illustrate their point, as follows: acute onset with complete recovery; progressive development with gradual recovery and residue; relapsing course; concomitant recovery with progression.

Various paralyses associated with cytoalbuminic dissociation have been found in infectious mononucleosis, brucellosis, diphtheria, antirabies inoculation, infectious

hepatitis, epidemic encephalitis, peritonsillar abscess, and other types of infectious disease.

This would indicate that the syndrome is only a symptomatic response to a basic physiopathologic process. Furtado suggested a "neuro-allergy of a peripheral form e.g. reaction of CNS against repeated infections of the Influenza virus." It is also noted that the eosinophil count is relatively high, and that there is a leukopenia and relative lmphocytosis. The rapid recovery suggests the process to be edema rather than inflammatory reaction.

The authors suggest that the Guillian-Barre syndrome is only a symptom-complex in the course of many diseases chiefly viral, in which the course and prognosis is extremely variable and unpredictable, and it is hoped that the syndrome will be eventually absorbed into already established diseases.

F.P.C.

Preparation and Use of Heterogenous Bone Grafts: Guilleminet, M., et al., Journal of Bone & Joint Surgery, Vol. 35-B, No. 4, Nov. 1953, 561–567.

This study was prompted by the relative inadequacy of bone banks in supplying human bone in sufficient quantity and quality, as well as previous failures in the use of heterogenous substitutes.

From preliminary experiments in 1949 and 1950 in the use of heterogenous grafts of calf bone, both refrigerated and non-refrigerated, cancellons and compact, in dogs and guinea pigs they considered that their results justified a trial of refrigerated calf bone in human surgery. In a series of 80 patients requiring arthrodesis of the hip, spinal fusion for Pott's disease, spondylolisthesis and sciatic pain, and filling of bone cavities, only 8 failed to take satisfactorily in association with sepis, results fully comparable with those obtained from autogenous grafts.

Concluded that if:

(1) Grafts were taken from younger animals (6-8 months).

(2) A particularly rigorous asceptic technique is followed (procedures necessary in the preparation of the graft allow many opportunities for contamination).

(3) Bone bed where graft is to lie is properly prepared:
  (i) Is healthy and vascular.
  (ii) Allows firm fixation of the graft.
  (iii) Allowance for growth and post-graft changes in the bed are made.
  (iv) Circular saw giving rise to heat necrosis of the bone is not used.

(4) Firm fixation of the graft with screws.

(5) Limb properly immobilized following procedure.

—Small heterogenous inlay grafts of frozen calf hind-limb bone are satisfactorily incorporated for human needs and in all ways comparable with the results obtained from autogenous grafts.

D. W. Wilson

Carcinoma of the Prostate: W. E. Kittredge; Postgraduate Medicine, Vol. 14, No. 5, 386, 1953.

The author states that the potential threat of carcinoma of the prostate occurs in 33% of males over 50.

There is no etiological relationship between other prostatic lesions and carcinoma. It usually occurs in men over 50 with the peak incidence between 55-85.

In 73% of cases it arises in the posterior lobe. In 9% in the lateral and 16% in the anterior aspect. Therefore the diseases should be readily recognizable by rectal examination. They grow rapidly or slowly and are anaplastic or adenocarcinomas. Metastases occur by lymphatics or the blood stream. Distant metastases are usually bony.

Symptoms are late and are those of urinary obstruction and/or metastasis. Diagnosis is made by rectal digital examination and the author stresses the fact that that a rectal examination should be done on all men in the cancer age group. Any small nodular, firm lesion within the gland should be considered carcinoma until proven otherwise. Later infiltration, fixation and obliteration of normal contour will occur. Other lesions such as calculi,

T.B. or chronic inflammatory lesions must be excluded before the diagnosis is made. Serum acid and alkaline phosphotase determinations aid diagnosis, the latter being elevated if bony metastases are present. Perineal biopsy may also help.

Only 5-10% of prostate carcinomas are recognized in the operable stage. He considers radical prostatectomy either perineal or retropubic the best. 50% of patients with radical prostatectomy are alive without recurrences after 5 years.

Palliative treatment consists of:

(i) Relief of urinary obstruction.

(ii) Hormone therapy with or without orchidectomy. This is not curative but it causes clinical improvement with prolongation of life. 45 mg. or more of stilboesterol daily are used by the author. Testosterone and cortisone may help in some cases. Bilateral adrenalectomy may also be beneficial in far advanced cases not responding to hormones. Deep X-ray therapy is of limited value. Radio-active gold isotopes injected directly into the gland are now being used in inoperable cases without recognizable distant metastases.

He concludes by stating that early diagnosis is the best cure.

R. M. Ehrlich

Anticoagulants in Treatment of Cardiac Infarction: American Heart Journal, December 1953, Vol. 46, No. 6, A. J. Kerwin.

Ever since the theoretical appreciation that heparin will inhibit the clotting mechanism and the experimental proof that mural thrombi will not form in heparinized dogs, anticoagulants have been tried in acute myocardial infarction with the hope of reducing the thrombo-embolic phenomena. Most series show decreased mortality rates in the treated group as compared to a control. Some authors failed to find this and consequently feel that anticoagulants are only indicated in poor "risk" patients. They argue that the expense and dangers of the therapy contraindicate it as a routine procedure.

The author points out the difficulties encountered in trying to formulate statistically satisfactory controls. In order that a statistical significance can be inferred between two groups, it must be established that they are identical except for the feature under study. Differences in sex percentages, ages, previous history of infarction, are all important. Unless they are balanced in both control and treated groups the results cannot be compared.

The author presents a series of 220 cases of cardiac infarction which were treated with Dicumarol and 81 cases treated with Danilone.

When the control series is compared with the treated group as a whole the mortality rate was decreased from 29.4% to 17.9%. The most marked difference was in the older age group.

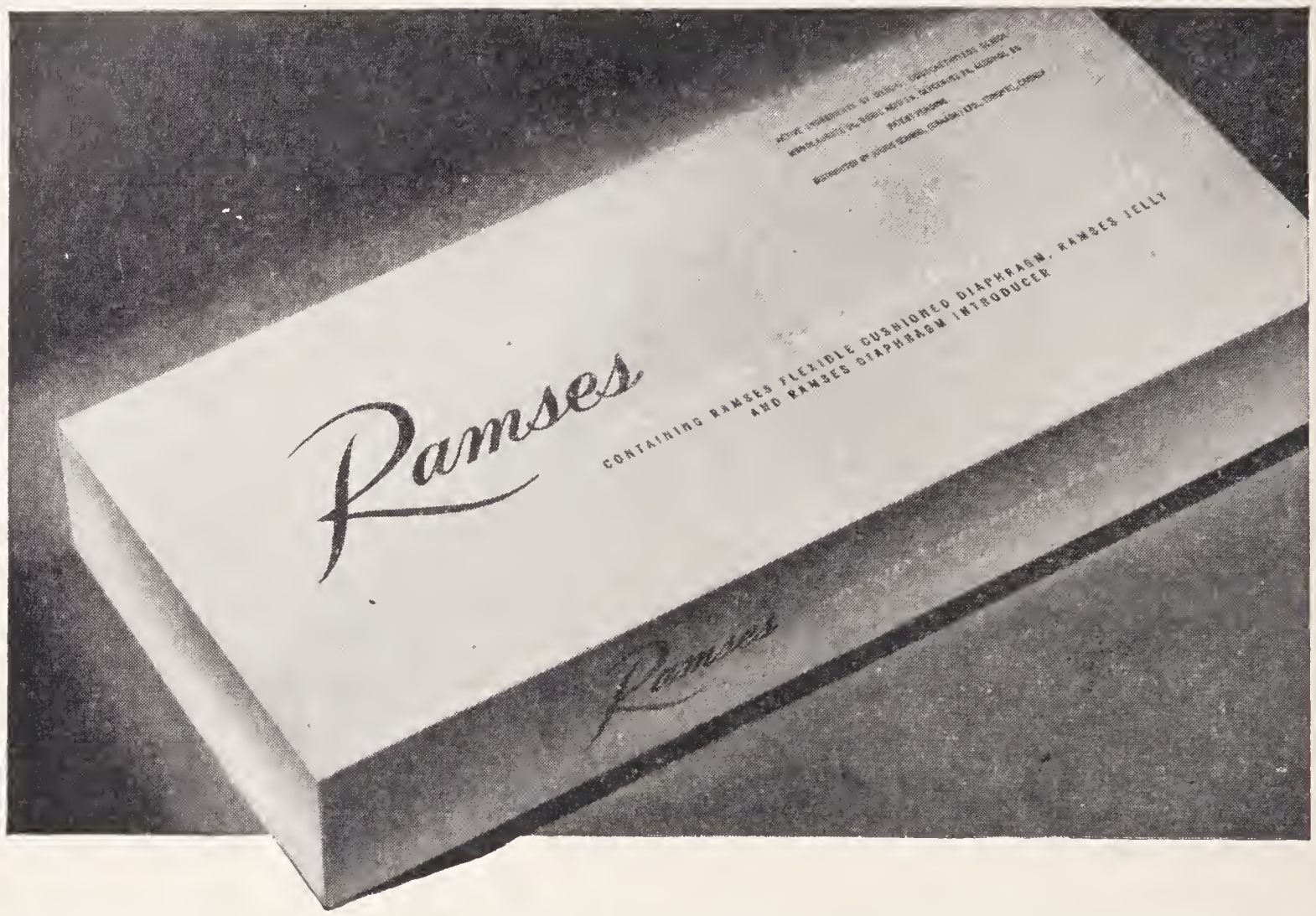
An interesting finding was that the most marked reduction was in patients who previously had failure. These patients showed a decrease in the death rate from 60.6% (controls) to 33.3% (treated). In patients without failure there was no difference in the death rate among treated and untreated patients.

Thrombo-embolic complications occurred in 20 percent of controls and in 7.6 percent of those receiving anticoagulants. This was most marked in the 50 age group and compatible reduction in complications was also evinced.

Can we divide the patients into poor "risks" or good "risks" early in the course of the disease and reserve anticoagulant therapy for the former. The author feels that with our present day clinical procedures this is impossible. Any of the good risk patients as adjudged by certain criteria, such as lack of complications, are just as likely to develop thrombo-embolic phenomena as any other patient.

The author concludes by stating that his results would indicate that anticoagulant therapy does influence the results favourably, most strikingly in patients with cardiac failure, and especially in the older age group.

J. D. Ainslie



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* 1. Dickinson, R. L.: Techniques of Conception Control, ed. 3, Baltimore, Williams & Wilkins Company, 1950, p.21. 2. Report to Council on Pharmacy and Chemistry, A.M.A.: J.A.M.A. 148: 50, Jan. 5, 1952. 3. Weisman, A. I.: Spermatozoa and Sterility, New York, Paul B. Hoeber, Inc., 1941, p.257.

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Coloured Red

Each sugar-coated tablet contains:

Ferrous sulphate (exsic.)	0.3 G.
Copper sulphate	1.6 mg.
Thiamine HCl	1 mg.
Riboflavin	1 mg.
Niacinamide	10 mg.
Ascorbic acid	25 mg.
Vitamin D	333 I.U.
Liver fraction 2, N.F.	67 mg.

For those cases of secondary anemia showing evidence of faulty erythrocyte maturation, Prohema Compound is available.

"PROHEMA" COMPOUND

Tablet No. 433 "Frosst"
Coloured Pink

Each sugar-coated tablet contains:

The same formula as tablet No. 432 with the addition of:

Vitamin B_{12}	2.5 mcg.
Folic acid	.67 mg.

DOSE: One tablet, three times daily.

MODES OF ISSUE: Bottles of 100 tablets.

Complete therapeutic information on request.

Frosst — SINCE 1899 — THE SYMBOL OF PROGRESS IN PHARMACEUTICAL RESEARCH

Charles E. Frosst & Co.
MONTREAL CANADA

for Quick Action!

in the Respiratory and Circulatory Emergencies
of Intravenous Barbiturate Anesthesia.

inject

COUNCIL ACCEPTED **Metrazol**

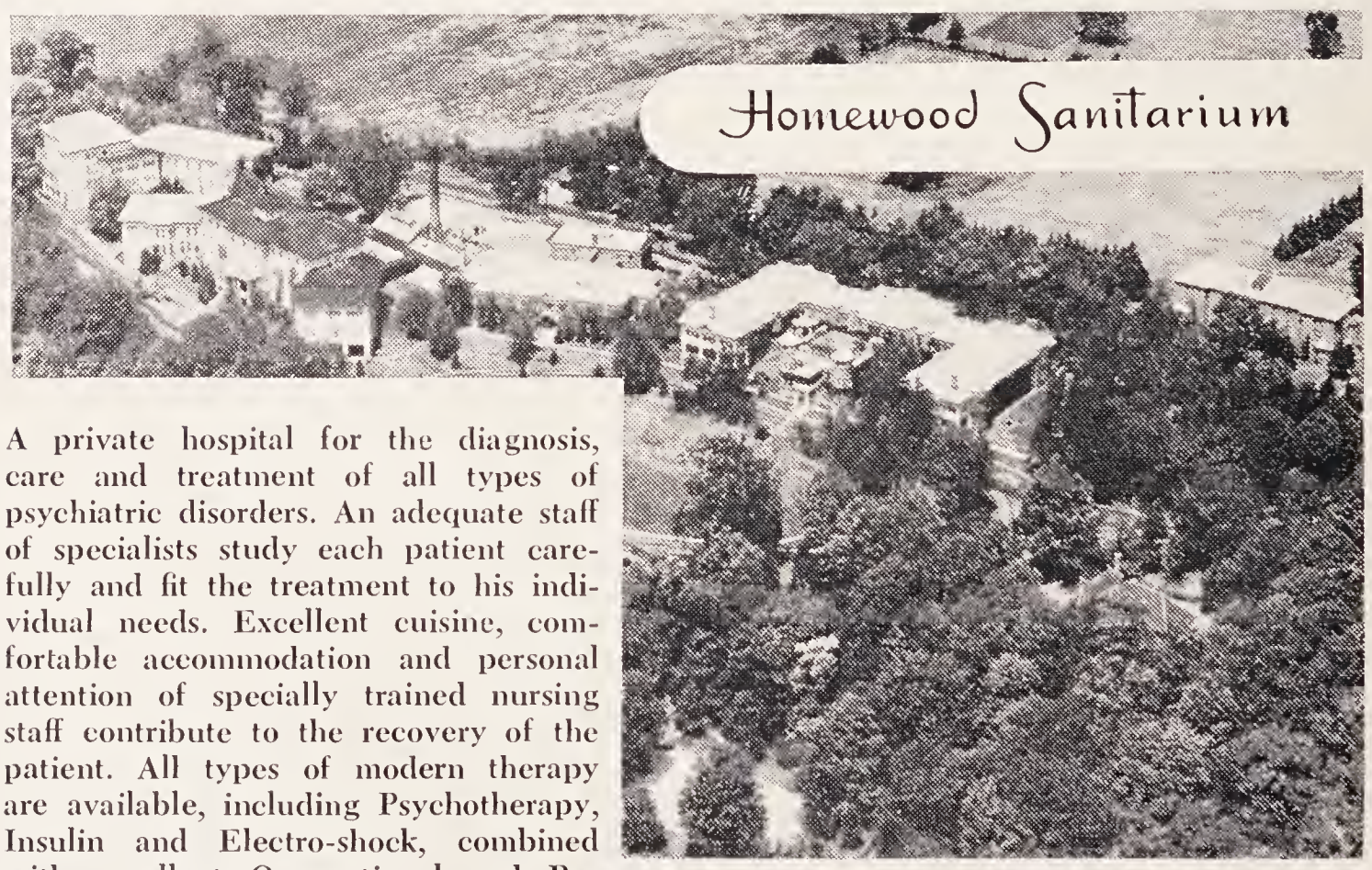
intravenously, intramuscularly, subcutaneously

In respiratory and other emergencies resulting from medullary depression during anesthesia. Ampules 1 and 3 cc., tablets, solution, powder.

Metrazol, pentamethylentetrazol, T. M. Reg. Canada

Product of Bilhuber-Knoll Corp., Orange, N. J.

MERCK & CO. Ltd. Selling Agents **MONTREAL**

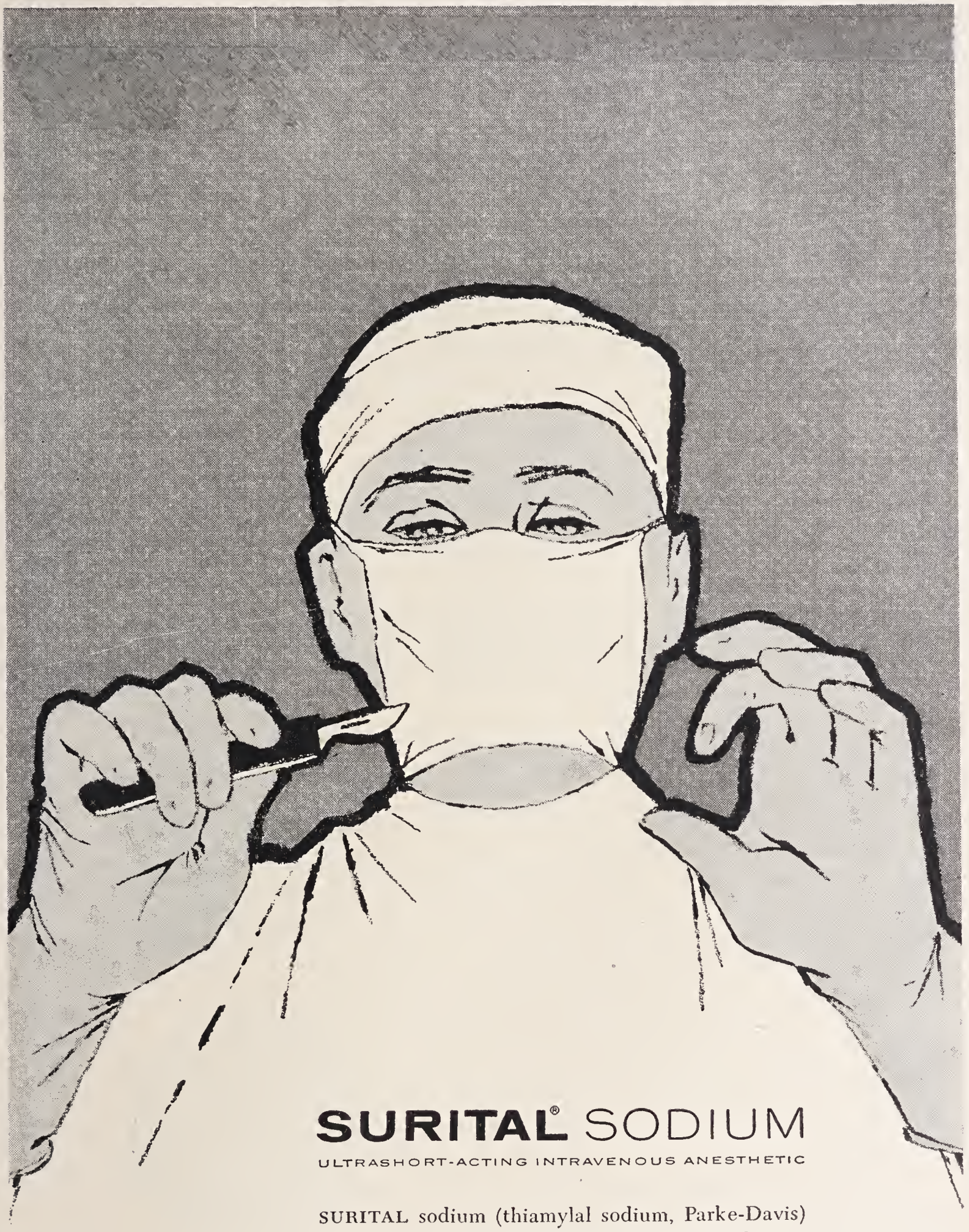


A private hospital for the diagnosis, care and treatment of all types of psychiatric disorders. An adequate staff of specialists study each patient carefully and fit the treatment to his individual needs. Excellent cuisine, comfortable accommodation and personal attention of specially trained nursing staff contribute to the recovery of the patient. All types of modern therapy are available, including Psychotherapy, Insulin and Electro-shock, combined with excellent Occupational and Recreational facilities.

The Sanitarium buildings, accommodating 225 patients, are situated in a very attractive setting within the confines of the City of Guelph. Visits by physicians and other interested parties are always welcomed. For further information write or telephone (Guelph 53).

A. L. MacKINNON, M.B.,
Medical Supt.

THE HOMEWOOD SANITARIUM OF
GUELPH, ONTARIO, LIMITED



SURITAL® SODIUM

ULTRASHORT-ACTING INTRAVENOUS ANESTHETIC

SURITAL sodium (thiamylal sodium, Parke-Davis) produces smooth anesthesia with rapid, quiet induction and prompt, pleasant recovery.

Detailed information on SURITAL sodium will be mailed you on request.

MEDICAMENTA VERA

Parke, Davis & Company, Ltd.

WALKERVILLE, ONTARIO

WHETHER THE REASONS ARE PHYSICAL OR PSYCHOLOGIC...

When for a physical or psychologic reason, the physician decides to depend on a vaginal jelly to protect the patient, he cannot do better than prescribe "RAMSES."*

The cohesive and adherent properties of "RAMSES" Vaginal Jelly† are of such high degree that the cervix remains occluded for as long as ten hours. "RAMSES" Vaginal Jelly, with its adjusted melting point, is not excessively lubricating or liquefying. "RAMSES" Vaginal Jelly exceeds the minimum immobilizing requirement of the Council on Pharmacy and Chemistry of the American Medical Association.

Used as directed, the plastic applicator deposits 5 cc. of "RAMSES" Vaginal Jelly over the cervical os.

ALSO AVAILABLE in regular 3-ounce and economy-size 5-ounce refill tubes.

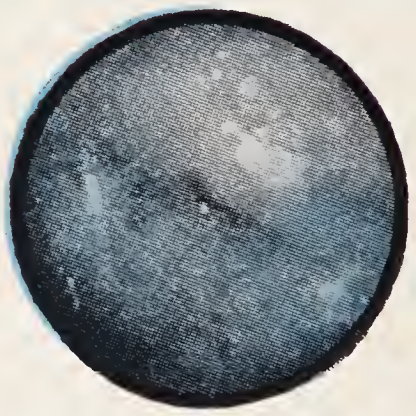


Photo taken after insertion of "RAMSES" Vaginal Jelly. Os occluded.

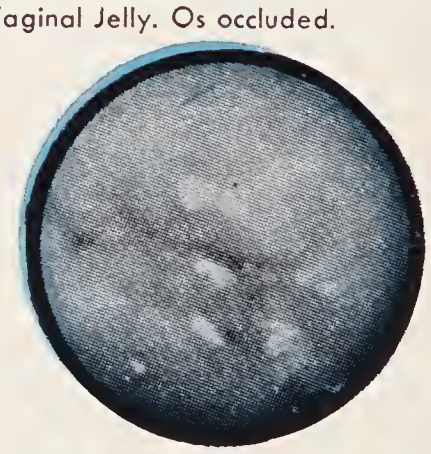


Photo taken ten hours later. Occlusion still manifest.

Jelly stained with methylene blue for photographic purposes.

JULIUS SCHMID (CANADA) LTD.

31 Teraulay Street • Toronto, Ontario

*The word "RAMSES" is a registered trademark. †Active Ingredients: Dodecaethyleneglycol Monolaurate 5%; Boric Acid 1%; Alcohol 5%.

Good diet insurance!

EACH VITULE CONTAINS:

Vitamin A Activity (from carotene, 1000 units: from fish-liver oils, 4000 units)	5000 I.U.
Vitamin D	500 I.U.
Thiamine Hydrochloride	1 mg.
Riboflavin	2 mg.
Niacinamide	10 mg.
d-Calcium Pantothenate	10 mg.
Pyridoxine	1 mg.
Ascorbic Acid	30 mg.
Mixed Tocopherols (antioxidant)	4 mg.
Liver Concentrate (derived from 2.5 gm. whole liver)	125 mg.
Brewers' Yeast	125 mg.

Wyeth
Registered Trade Mark

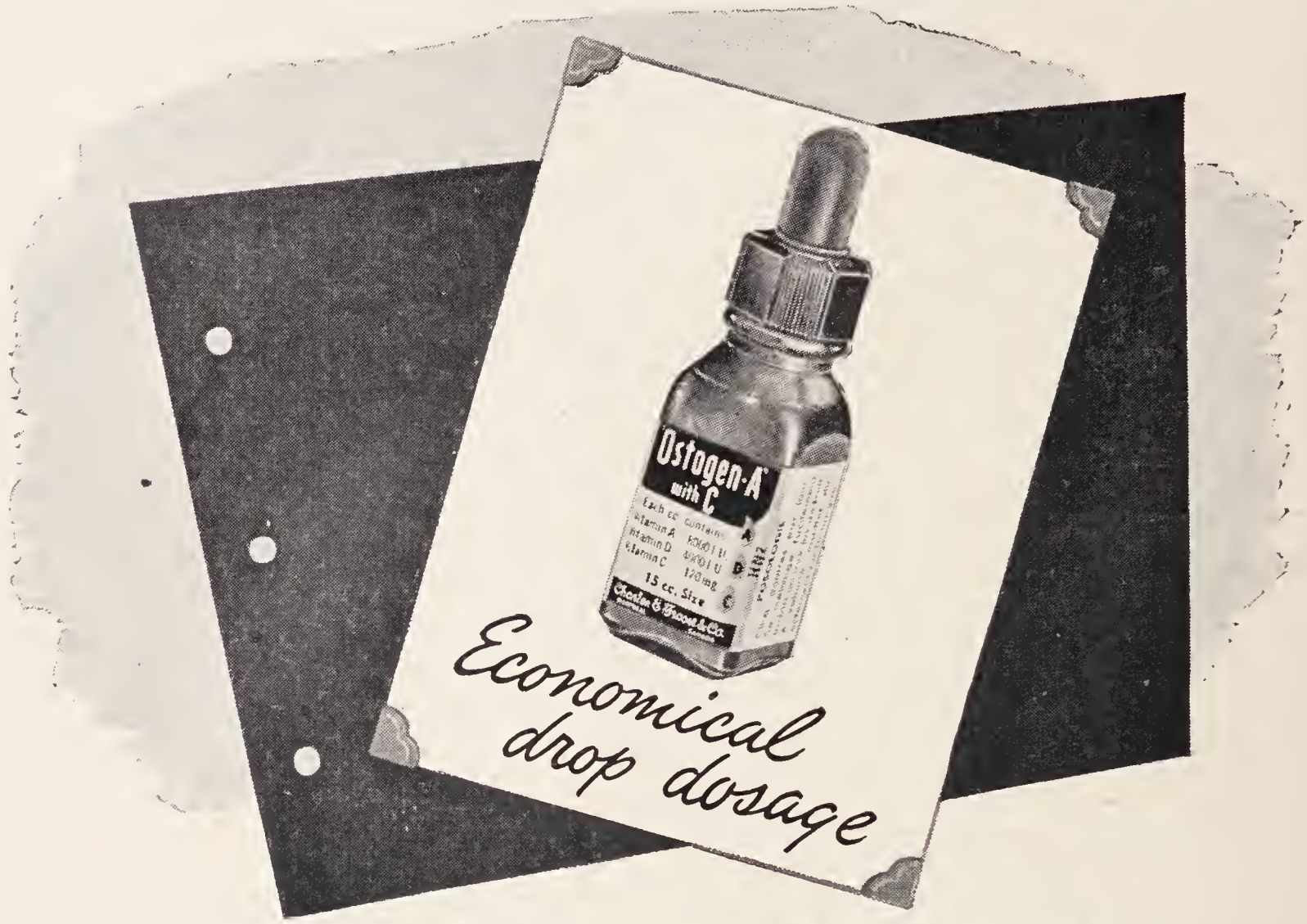
VITULES MULTIVITAMIN CAPSULES

SUGGESTED DOSAGE:

MAINTENANCE: One Vitule daily.

THERAPEUTIC: Three or more Vitules daily. The rapid excretion of water soluble vitamins suggests a daily intake in divided doses to ensure maximum utilization.

A PAGE FROM THE "Frosst" ALBUM



"Ostogen-A with C"

VITAMINS A, D AND C

- Aqueous vehicle enhances absorption and utilization
- Mixes readily with milk or other liquids
- Pleasant flavour — accepted by all children

Frosst
SINCE 1899 THE SYMBOL OF PROGRESS IN PHARMACEUTICAL RESEARCH

"OSTOGEN-A with C"

Each 5 drop dose (0.25 cc.) contains:

Vitamin A palmitate 2000 Int. units
Vitamin D.....1000 Int. units
Vitamin C..... 30 mg.

DOSE: Five drops daily.

MODES OF ISSUE: Bottles of 8,15 and 30 cc., with calibrated dropper.

Charles E. Frosst & Co.
MONTREAL CANADA

codophen

ANALGESIC SEDATIVE

now available in 4 strengths

*M is for Milder

*R is for Regular

*S is for Stronger

*Paed

Prescribe as:

Codophen-M
C.T. No. 255

Contains per tablet:
Acetylsalicylic Acid 3 gr.
Phenacetine ..... 2 gr.
Caffeine Citrate..... ¼ gr.
Codeine Phosphate ⅛ gr.

Codophen-R
(formerly Codophen)
C.T. No. 260

Contains per tablet:
Acetylsalicylic Acid 3 gr.
Phenacetine ..... 2 gr.
Caffeine Citrate..... ¼ gr.
Codeine Phosphate ¼ gr.

Codophen-S
(formerly Codophen Stronger)
C.T. No. 260A

Contains per tablet:
Acetylsalicylic Acid 3 gr.
Phenacetine ..... 2 gr.
Caffeine Citrate..... ¼ gr.
Codeine Phosphate ½ gr.

Codophen Paediatric
C.T. No. 259

Contains per tablet:
Acetylsalicylic Acid ⅞ gr.
Phenacetine ..... ⅝ gr.
Caffeine Citrate..... ⅛ gr.
Codeine Phosphate 1/16 gr.

Codophen is indicated for symptomatic relief of pain in muscular and rheumatic conditions, lumbago, neuritis, neuralgia, migraine and febrile conditions.

How supplied: Bottles of 100, 500 and 1,000.

THE E.B. SHUTTLEWORTH CHEMICAL CO. LTD., TORONTO, CANADA

Pharmacy

an ancient and honorable profession

English Seventeenth Century Apothecary Shop (The Bettman Archive)

Entrust your needs to a specialist

LET THE PHARMACIST DO *ALL* YOUR DISPENSING

Pharmacy, in meeting the needs of modern medicine, has developed into a highly complex and specialized arm of the medical profession. Most doctors, knowing this, are saving themselves the time and expense of attempting to run a complete private dispensary. A stroke of the pen or a phone call — and they entrust all their dispensing needs with justifiable confidence to their skilled professional aide — the friendly pharmacist.

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